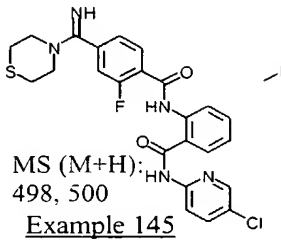
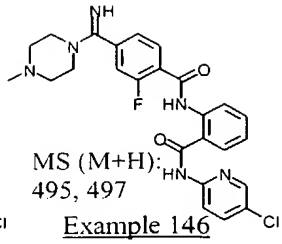


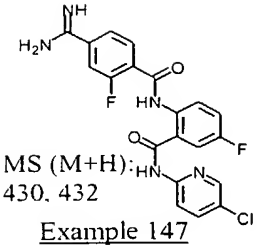
MS (M+H): 498, 500

Example 145



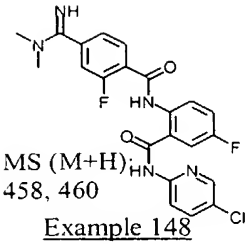
MS (M+H): 495, 497

Example 146



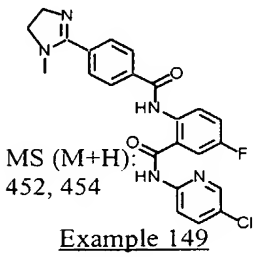
MS (M+H): 430, 432

Example 147



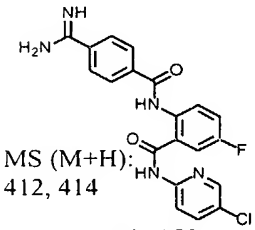
MS (M+H): 458, 460

Example 148



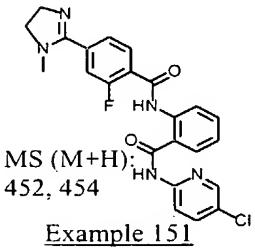
MS (M+H): 452, 454

Example 149



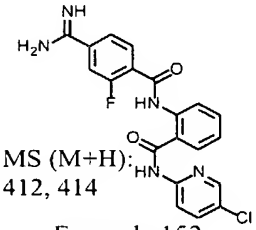
MS (M+H): 412, 414

Example 150



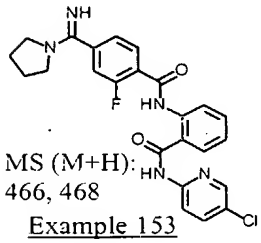
MS (M+H): 452, 454

Example 151



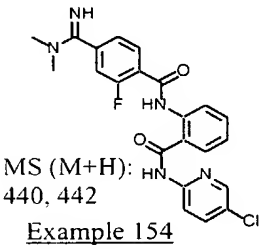
MS (M+H): 412, 414

Example 152



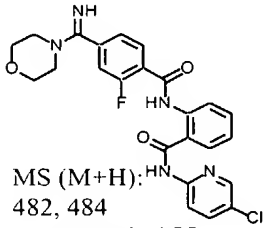
MS (M+H): 466, 468

Example 153



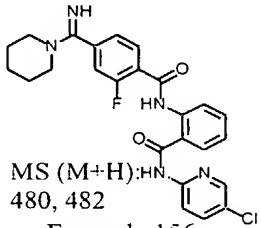
MS (M+H): 440, 442

Example 154



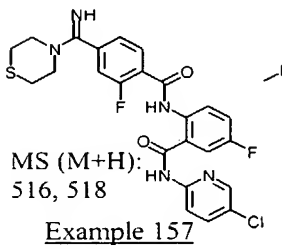
MS (M+H): 482, 484

Example 155



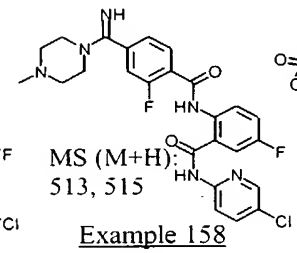
MS (M+H): 480, 482

Example 156



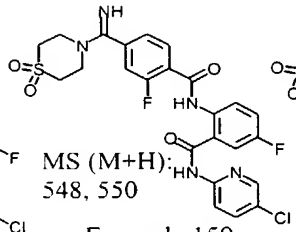
MS (M+H): 516, 518

Example 157



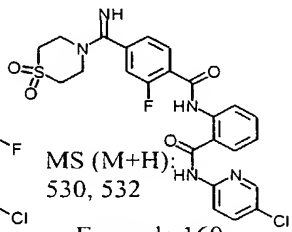
MS (M+H): 513, 515

Example 158



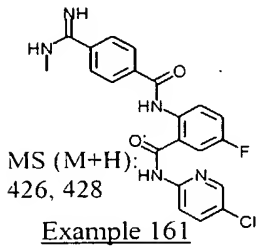
MS (M+H): 548, 550

Example 159



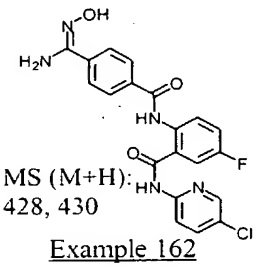
MS (M+H): 530, 532

Example 160



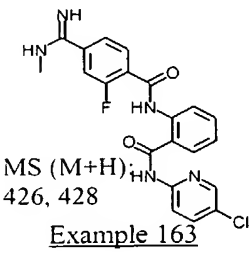
MS (M+H): 426, 428

Example 161



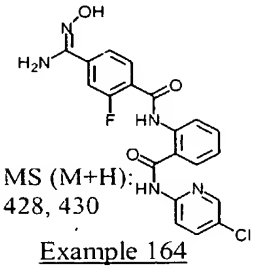
MS (M+H): 428, 430

Example 162



MS (M+H): 426, 428

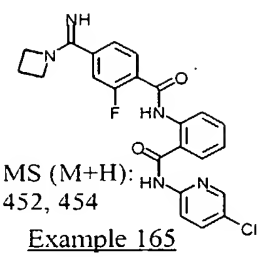
Example 163

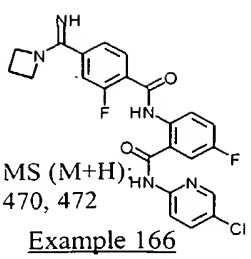


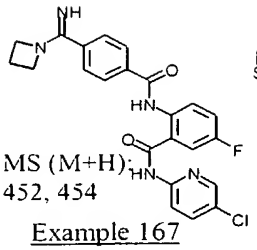
MS (M+H): 428, 430

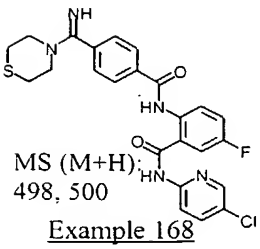
Example 164

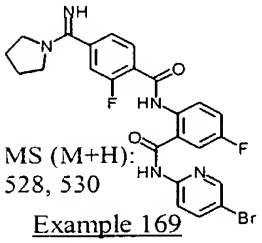
5

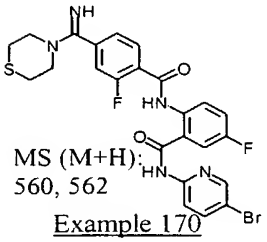

MS (M+H): 452, 454
Example 165

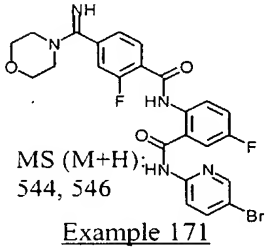

MS (M+H): 470, 472
Example 166

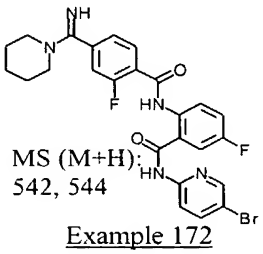

MS (M+H): 452, 454
Example 167

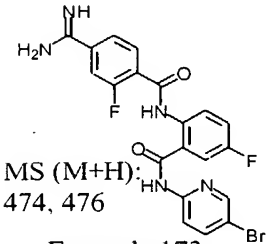

MS (M+H): 498, 500
Example 168

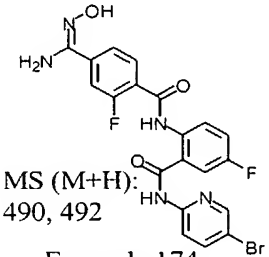

MS (M+H): 528, 530
Example 169

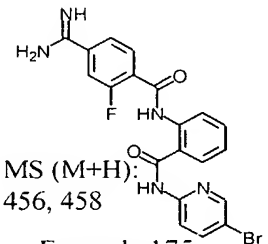

MS (M+H): 560, 562
Example 170

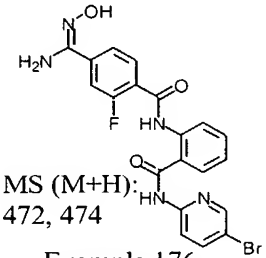

MS (M+H): 544, 546
Example 171

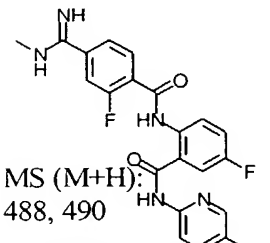

MS (M+H): 542, 544
Example 172

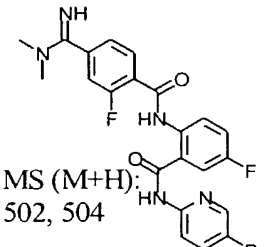

MS (M+H): 474, 476
Example 173

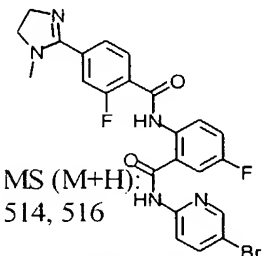

MS (M+H): 490, 492
Example 174

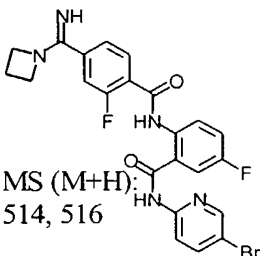

MS (M+H): 456, 458
Example 175

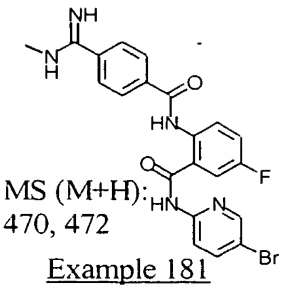

MS (M+H): 472, 474
Example 176


MS (M+H): 488, 490
Example 177


MS (M+H): 502, 504
Example 178

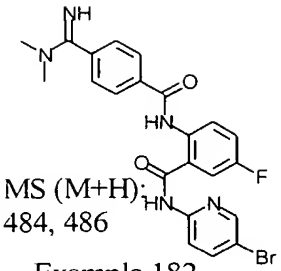

MS (M+H): 514, 516
Example 179


MS (M+H): 514, 516
Example 180



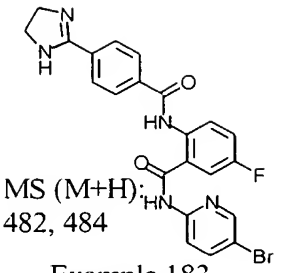
MS (M+H): 470, 472

Example 181



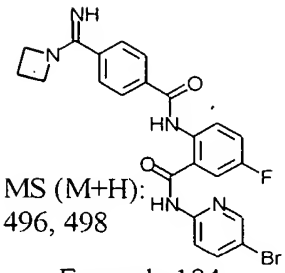
MS (M+H): 484, 486

Example 182



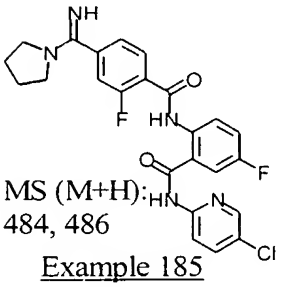
MS (M+H): 482, 484

Example 183



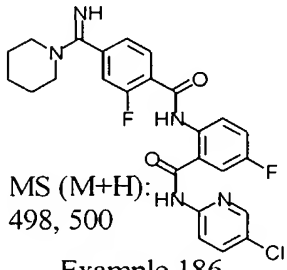
MS (M+H): 496, 498

Example 184



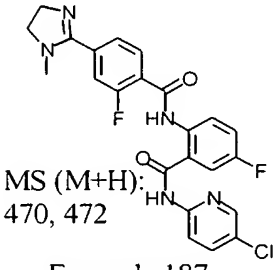
MS (M+H): 484, 486

Example 185



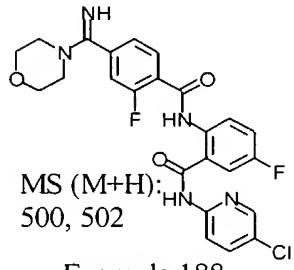
MS (M+H): 498, 500

Example 186



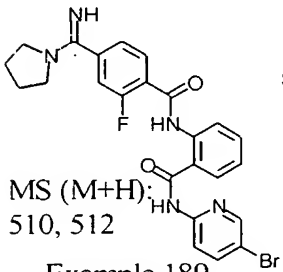
MS (M+H): 470, 472

Example 187



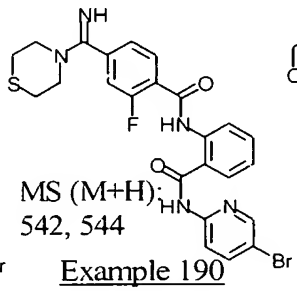
MS (M+H): 500, 502

Example 188



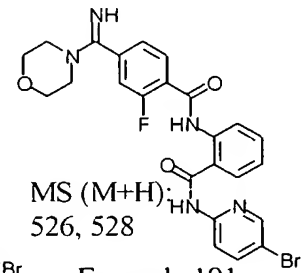
MS (M+H): 510, 512

Example 189



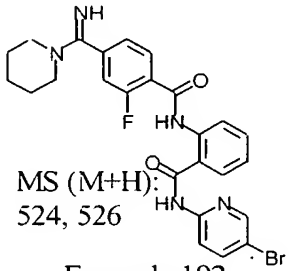
MS (M+H): 542, 544

Example 190



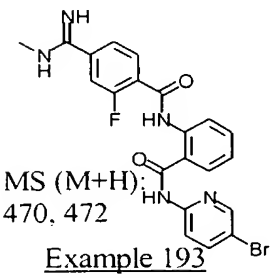
MS (M+H): 526, 528

Example 191



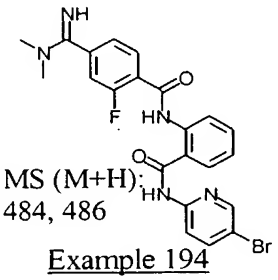
MS (M+H): 524, 526

Example 192



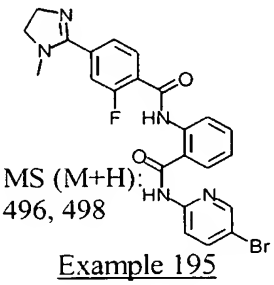
MS (M+H): 470, 472

Example 193



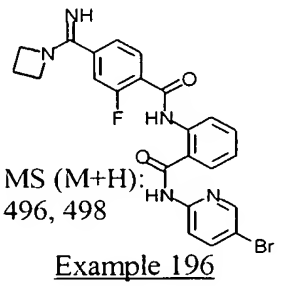
MS (M+H): 484, 486

Example 194



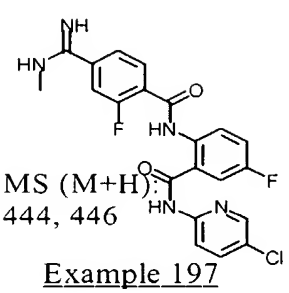
MS (M+H): 496, 498

Example 195



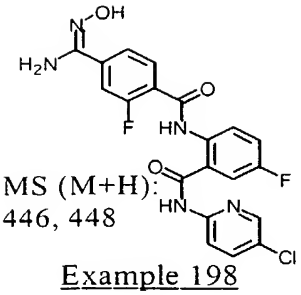
MS (M+H): 496, 498

Example 196



MS (M+H)$^+$: 444, 446

Example 197

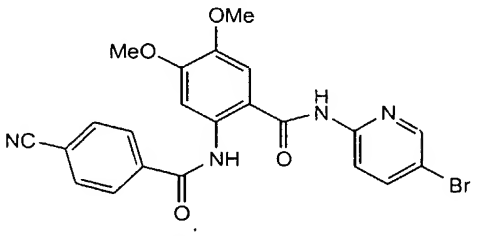


MS (M+H)$^+$: 446, 448

Example 198

Example 199

N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}(4-cyanophenyl)carboxamide



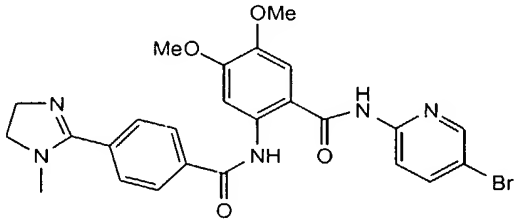
To a solution of 4,5-dimethoxy-2-nitrobenzoic acid (2.2gm, 10mmol) and 2-amino-5-bromopyridine (2.4gm, 14mmol) in anhydrous pyridine (50mL) at 0°C was added $POCl_3$ (1.9mL, 20mmol). After stirring at room temperature for 30min, the reaction was complete. The mixture was concentrated and diluted with EtOAc (200mL). The organic solution was washed with brine, dried and evaporated to give intermediate compound **1** (3.0gm, 80%). MS found for $C_{14}H_{12}BrN_3O_5$ $(M+H)^+$: 382.00, 383.95.

A mixture of intermediate compound **1** (320mg, 0.83mmol) and $SnCl_2 \cdot 2H_2O$ (900mg, 4.0mmol) in EtOAc (10mL) was refluxed for 1 hour. Reduction completed. The solid was filtered through a celite bed. The filtrate was diluted with EtOAc (50mL), and the red solution was washed with 1N aq. NaOH solution (x3) and brine, dried and evaporated to give intermediate compound **2** (230mg, 78%). MS found for $C_{14}H_{14}BrN_3O_3$ $(M+H)^+$: 352.00, 354.05.

To a solution of intermediate compound **2** (200mg, 0.57mmol) in a mixture of pyridine (3mL) and DCM (10mL) was added 4-cyanobenzoyl chloride (140mg, 0.85mmol). Precipitate formed immediately and the reaction was complete. The solid was collected by filtration and washed with DCM. After drying in vacco, the titled compound was obtained as a yellow solid in 70% yield (190mg). MS found for $C_{22}H_{17}BrN_4O_4$ $(M+H)^+$: 481.00, 483.00.

Example 200

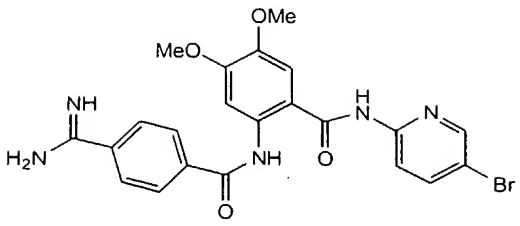
(4,5-dimethoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino}phenyl)-N-(5-bromo(2-pyridyl))carboxamide



To a solution of compound obtained in Example 259 (100mg, 0.20mmol) in 10% Et_3N/pyridine (10mL) at 0°C was bubbled dry H_2S gas to saturation. The mixture was stirred at ambient temperatures overnight, and the conversion was complete. The solvent was removed to dryness, and the residue was suspended in anhydrous acetone (10mL), followed by addition of MeI (1mL). The reaction mixture was refluxed for 1 hour. The solvent was removed by rotary evaporation. To the residue was added anhydrous MeOH (10mL) and N-methylethylenediamine (1mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound. MS found for $C_{25}H_{24}BrN_5O_4$ $(M+H)^+$: 538.1, 540.1.

Example 201

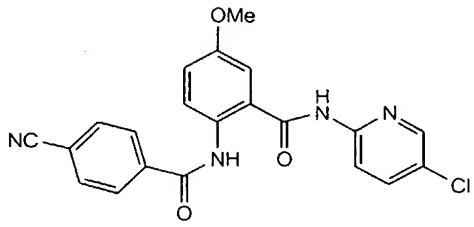
4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}carbamoyl)-benzenecarboxamidine



The title compound was obtained according to the procedure previously described. MS found for $C_{22}H_{20}BrN_5O_4$ $(M+H)^+$: 498.1, 500.0.

Example 202

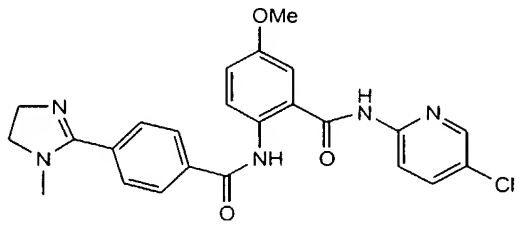
N-(5-chloro(2-pyridyl))\{2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl\}-carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{21}H_{15}ClN_4O_3$ $(M+H)^+$: 407.0.

Example 203

N-(5-chloro(2-pyridyl))(5-methoxy-2-\{[4-(1-methyl(2-imidazolin-2-yl))phenyl]-carbonylamino\}phenyl)carboxamide

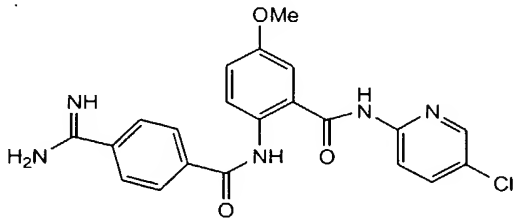


To the suspension of the compound Example 262 (100mg) in a mixture of anhydrous MeOH (5mL) and EtOAc (5mL) at 0°C was bubbled anhydrous HCl gas to saturation. The mixture was stirred at ambient temperatures overnight. The conversion completed. The solvent was evaporated to dryness. The residue was dissolved in anhydrous MeOH (10mL), followed by addition of N-methylethylenediamine (1mL).

The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound 263. MS found for $C_{24}H_{22}ClN_5O_3$ $(M+H)^+$: 464.

Example 204

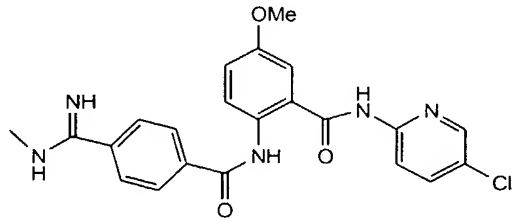
4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzene-carboxamidine



The title compound was obtained according to the procedure previously described. MS found for $C_{21}H_{18}ClN_5O_3$ $(M+H)^+$: 424.

Example 205

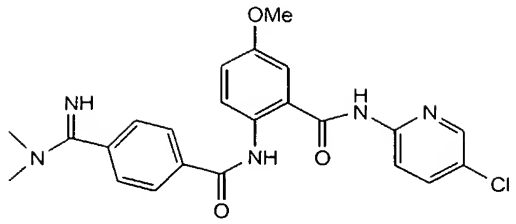
N-(5-chloro(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl}carbonylamino)-5-methoxyphenyl]carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{22}H_{20}ClN_5O_3$ $(M+H)^+$: 438.

Example 206

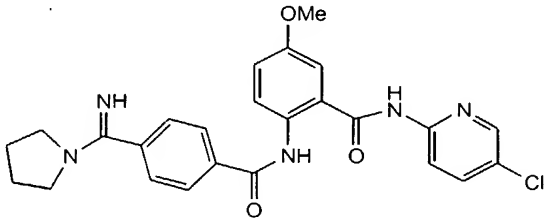
[2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{23}H_{22}ClN_5O_3$ $(M+H)^+$: 452.

Example 207

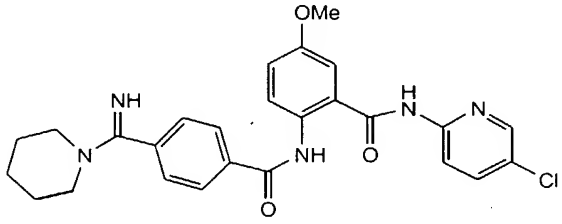
N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{25}H_{24}ClN_5O_3$ $(M+H)^+$: 478.

Example 208

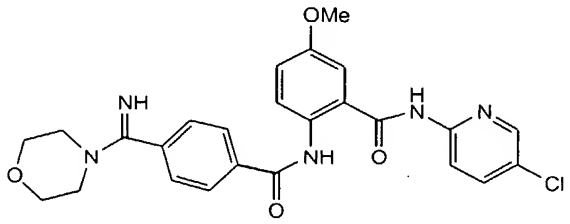
N-(5-chloro(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{26}H_{26}ClN_5O_3$ $(M+H)^+$: 492.

Example 209

N-(5-chloro(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamin}-5-methoxyphenyl)carboxamide

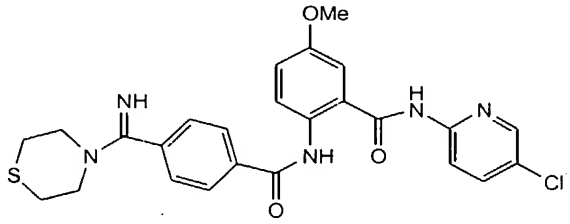


The title compound was obtained according to the procedure previously described.

MS found for $C_{25}H_{24}ClN_5O_4$ $(M+H)^+$: 494.1.

Example 210

N-(5-chloro(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

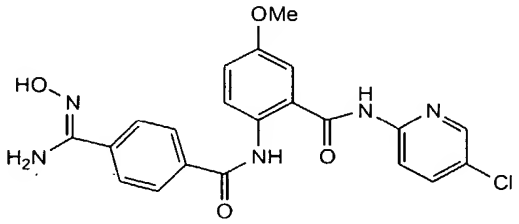


The title compound was obtained according to the procedure previously described.

MS found for $C_{25}H_{24}ClN_5O_3S$ $(M+H)^+$: 510.

Example 211

(2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide

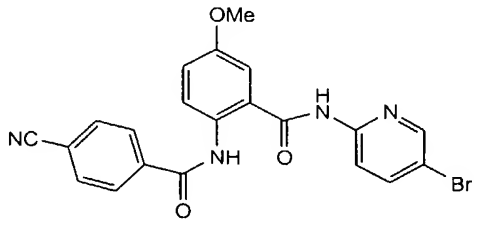


To a suspension of compound N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide (150mg) in EtOH (10mL) was added hydroxyamine hydrochloride (80mg) and Et_3N (200μL). The

mixture was stirred at 60°C overnight and the reaction was complete. The solvent was evaporated and the crude material was purified by RP-HPLC to give the title compound. MS found for $C_{21}H_{18}ClN_5O_4$ $(M+H)^+$: 440.1.

Example 212

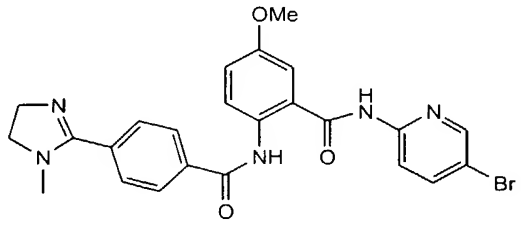
N-(5-bromo(2-pyridyl))\{2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl\}carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{21}H_{15}BrN_4O_3$ $(M+H)^+$: 451.00, 453.00.

Example 213

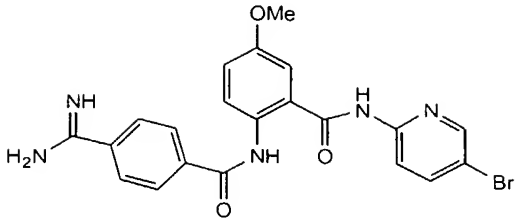
N-(5-bromo(2-pyridyl))(5-methoxy-2-\{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino\}phenyl)carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{24}H_{22}BrN_5O_3$ $(M+H)^+$: 508, 510.

Example 214

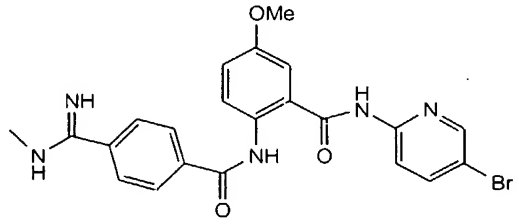
4-(N-\{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4-methoxyphenyl\}carbamoyl)benzenecarboxamidine



The title compound was obtained according to the procedure previously described. MS found for $C_{21}H_{18}BrN_5O_3$ $(M+H)^+$: 468.05, 470.00.

Example 215

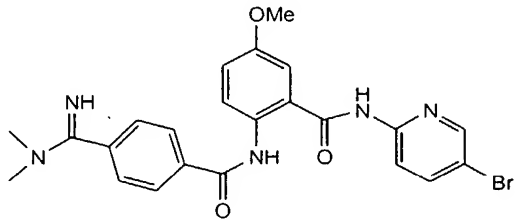
N-(5-bromo(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl}carbonylamino)-5-methoxyphenyl]carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{22}H_{20}BrN_5O_3$ $(M+H)^+$: 482, 484.

Example 216

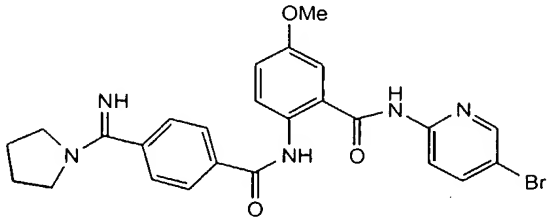
[2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-bromo(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{23}H_{22}BrN_5O_3$ $(M+H)^+$: 496.1, 498.1.

Example 217

N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

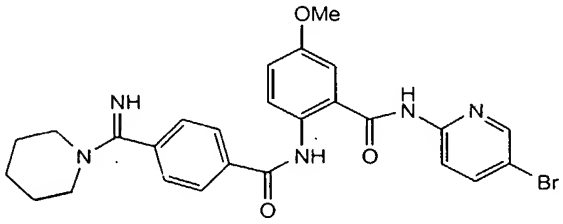


The title compound was obtained according to the procedure previously described.

MS found for $C_{25}H_{24}BrN_5O_3$ $(M+H)^+$: 522, 524.

Example 218

N-(N-(5-bromo(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

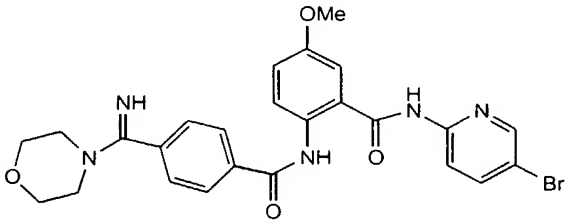


The title compound was obtained according to the procedure previously described.

MS found for $C_{26}H_{26}BrN_5O_3$ $(M+H)^+$: 536.1, 538.1.

Example 219

N-(5-bromo(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

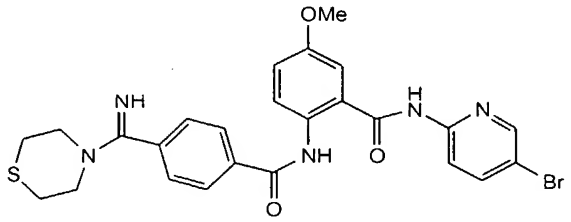


The title compound was obtained according to the procedure previously described.

MS found for $C_{25}H_{24}BrN_5O_4$ $(M+H)^+$: 538.1, 540.1.

Example 220

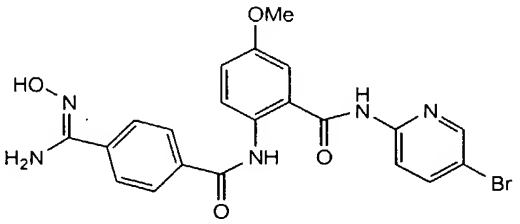
N-(5-bromo(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{25}H_{24}BrN_5O_3S$ $(M+H)^+$: 554.1, 556.05.

Example 221

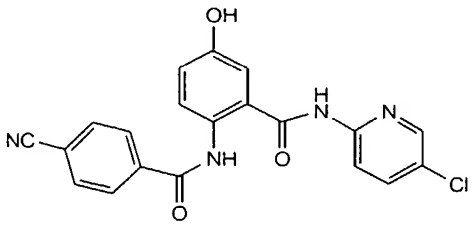
(2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{21}H_{18}BrN_5O_4$ $(M+H)^+$: 484.1, 486.0.

Example 222

N-(5-chloro(2-pyridyl))\{6-[(4-cyanophenyl)carbonylamino]-3-hydroxyphenyl\}carboxamide

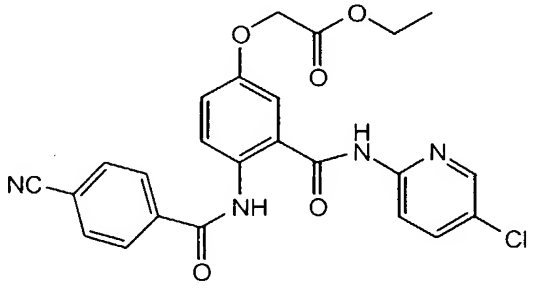


To a suspension of compound N-(5-chloro(2-pyridyl))\{2-[(4-cyanophenyl)-carbonylamino]-5-methoxyphenyl\}carboxamide (500mg, 1.2mmol) in DCM (100mL)

at -78°C was added BBr_3 (2mL). The mixture was stirred at ambient temperatures for 72 hours. The solid was collected by filtration and was washed by DCM and water, dried under vacuum. The filtrate was concentrated and extracted with EtOAc. The organic extract was washed with brine, dried and evaporated. The resulting solid was combined with the solid obtained from filtration to give the title compound. Total yield is 90% (430mg). MS found for $C_{20}H_{13}ClN_4O_3$ $(M+H)^+$: 393.0.

Example 223

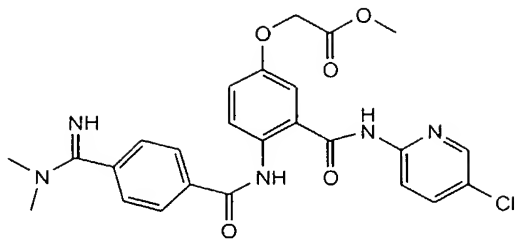
ethyl 2-{3-[N-(5-chloro(2-pyridyl))carbamoyl]-4-[(4-cyanophenyl)carbonylamino]-phenoxy}acetate



To a mixture of compound N-(5-chloro(2-pyridyl)){6-[(4-cyanophenyl)-carbonylamino]-3-hydroxyphenyl}carboxamide (50mg, 0.13mmol) and Cs_2CO_3 (83mg, 0.25mmol) in DMF (1mL) at room temperature was added ethyl bromoacetate (15μL, 0.13mmol). The mixture was stirred for 1 hour before diluted with EtOAc (20mL) and water (10mL). The organic layer was washed with brine dried and evaporated to give 70mg of the crude compound, which was used without farther purification. MS found for $C_{24}H_{19}ClN_4O_5$ $(M+H)^+$: 479.0.

Example 224

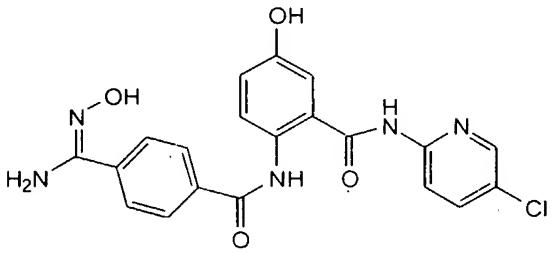
methyl 2-[4-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-3-[N-(5-chloro(2-pyridyl))carbamoyl]phenoxy]acetate



The title compound was obtained according to the procedure previously described. MS found for $C_{25}H_{24}ClN_5O_5$ $(M+H)^+$: 510.1.

Example 225

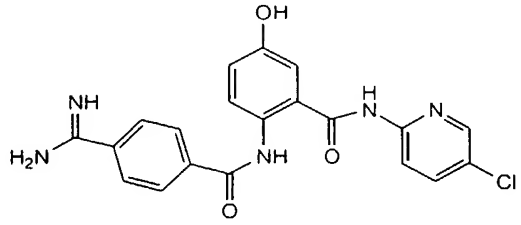
(6-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-3-hydroxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{20}H_{16}ClN_5O_4$ $(M+Na)^+$: 448.0.

Example 226

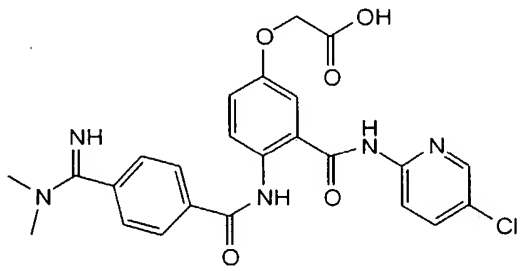
4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine



The title compound was obtained according to the procedure previously described. MS found for $C_{20}H_{16}ClN_5O_3$ $(M+H)^+$: 410.1.

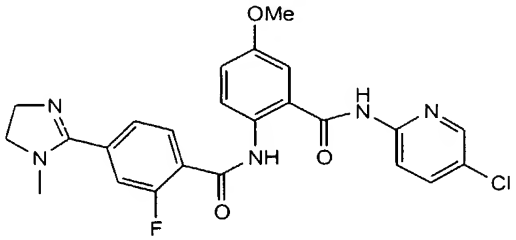
Example 227

4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine



To a solution of Example 284 (10mg) in MeOH (1mL) was added 50μL of 1N aq. LiOH solution. The mixture was stirred for 1 hour and purified by RP-HPLC to give the title compound. MS found for $C_{24}H_{22}ClN_5O_5$ $(M+H)^+$: 496.

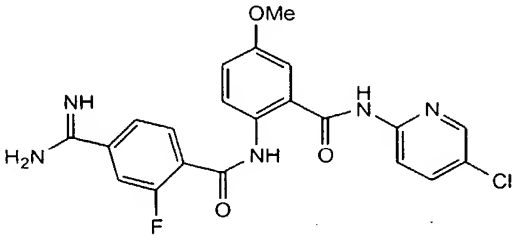
Example 228



$C_{24}H_{21}ClFN_5O_3$
Exact Mass. 481.13
Mol. Wt.: 481.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_3$: $(M+H)^+$: 482.1.

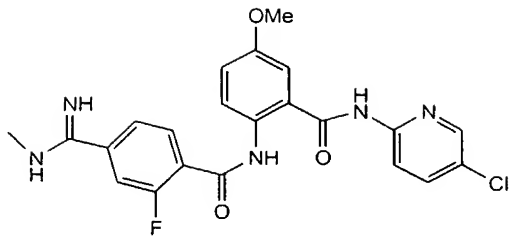
Example 229



$C_{21}H_{17}ClFN_5O_3$
Exact Mass: 441.10
Mol. Wt.: 441.84

The title compound was synthesized according to the procedure described previously. MS found for $C_{21}H_{17}ClFN_5O_3$: $(M+H)^+$: 442.1.

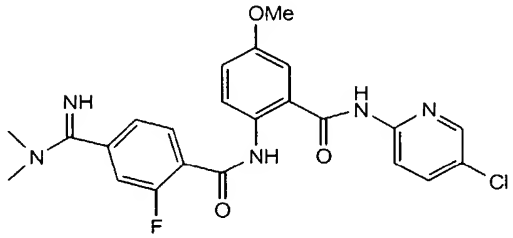
Example 230



$C_{22}H_{19}ClFN_5O_3$
Exact Mass: 455.12
Mol. Wt.: 455.87

The title compound was synthesized according to the procedure described previously. MS found for $C_{22}H_{19}ClFN_5O_3$: $(M+H)^+$: 456.1.

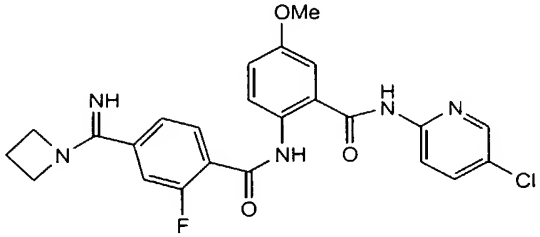
Example 231



$C_{23}H_{21}ClFN_5O_3$
Exact Mass: 469.13
Mol. Wt.: 469.90

The title compound was synthesized according to the procedure described previously. MS found for $C_{23}H_{21}ClFN_5O_3$: $(M+H)^+$: 470.1.

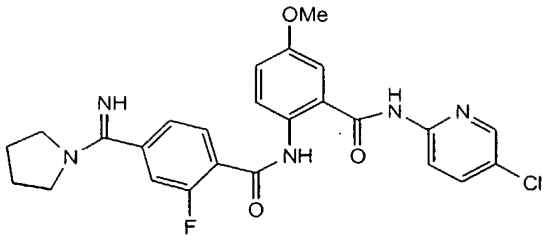
Example 232



$C_{24}H_{21}ClFN_5O_3$
Exact Mass: 481.13
Mol. Wt.: 481.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_3$: $(M+H)^+$: 482.1.

Example 233

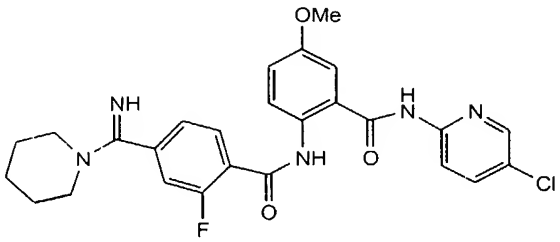


$C_{25}H_{23}ClFN_5O_3$
Exact Mass: 495.15
Mol. Wt.: 495.93

The title compound was synthesized according to the procedure described previously.

MS found for $C_{25}H_{23}ClFN_5O_3$: $(M+H)^+$: 496.1.

Example 234

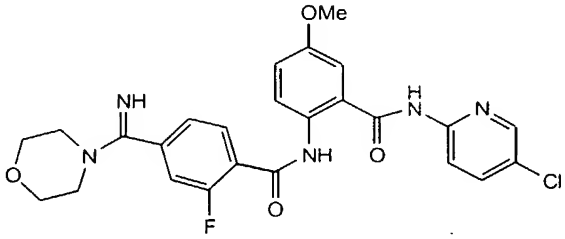


$C_{26}H_{25}ClFN_5O_3$
Exact Mass: 509.16
Mol. Wt.: 509.96

The title compound was synthesized according to the procedure described previously.

MS found for $C_{26}H_{25}ClFN_5O_3$: $(M+H)^+$: 510.2.

Example 235

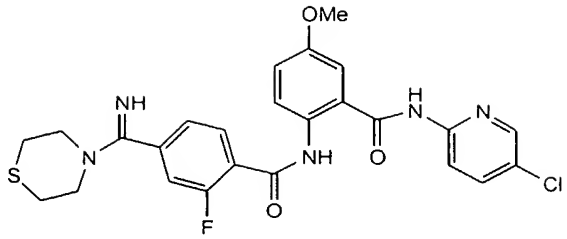


$C_{25}H_{23}ClFN_5O_4$
Exact Mass: 511.14
Mol. Wt.: 511.93

The title compound was synthesized according to the procedure described previously.

MS found for $C_{25}H_{23}ClFN_5O_4$: $(M+H)^+$: 512.2.

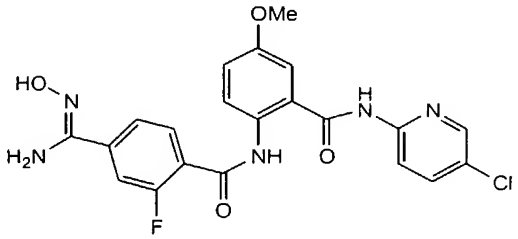
Example 236



$C_{25}H_{23}ClFN_5O_3S$
Exact Mass: 527.12
Mol. Wt.: 528.00

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{23}ClFN_5O_3S$: $(M+H)^+$: 528.1.

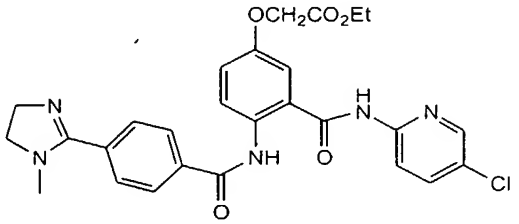
Example 237



$C_{21}H_{17}ClFN_5O_4$
Exact Mass: 457.10
Mol. Wt.: 457.84

The title compound was synthesized according to the procedure described previously. MS found for $C_{21}H_{17}ClFN_5O_4$: $(M+H)^+$: 458.1.

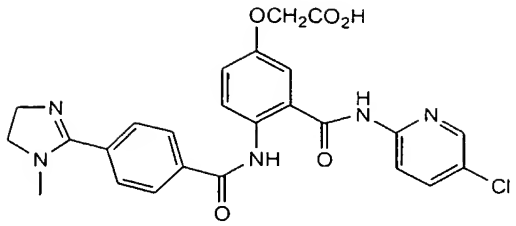
Example 238



$C_{27}H_{26}ClN_5O_5$
Exact Mass: 535.16
Mol. Wt.: 535.98

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

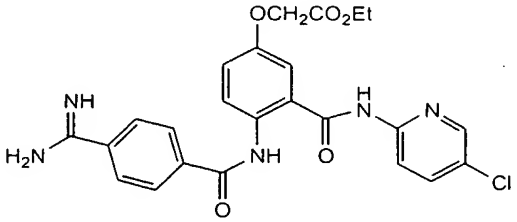
Example 239



$C_{25}H_{22}ClN_5O_5$
Exact Mass: 507.13
Mol. Wt.: 507.93

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{22}ClN_5O_5$: $(M+H)^+$: 508.1.

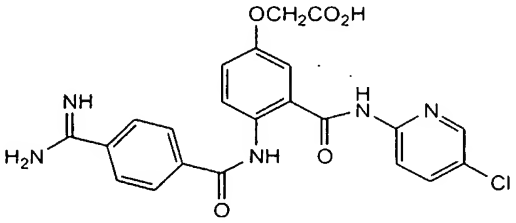
Example 240



$C_{24}H_{22}ClN_5O_5$
Exact Mass: 495.13
Mol. Wt.: 495.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{22}ClN_5O_5$: $(M+H)^+$: 496.1.

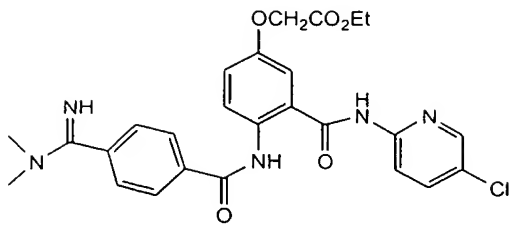
Example 241



$C_{22}H_{18}ClN_5O_5$
Exact Mass: 467.10
Mol. Wt.: 467.86

The title compound was synthesized according to the procedure described previously. MS found for $C_{22}H_{18}ClN_5O_5$: $(M+H)^+$: 468.1.

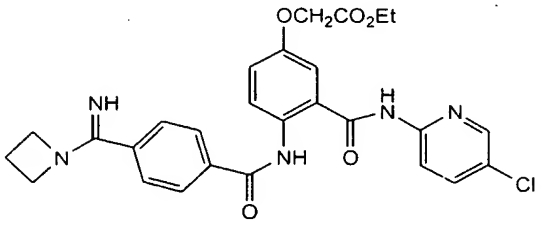
Example 242



$C_{26}H_{26}ClN_5O_5$
Exact Mass: 523.16
Mol. Wt.: 523.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{26}ClN_5O_5$: $(M+H)^+$: 524.2.

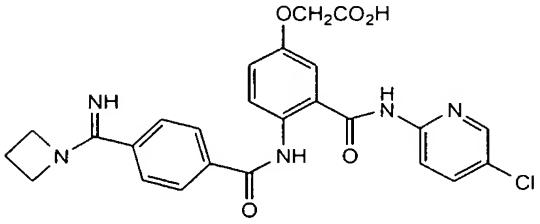
Example 243



$C_{27}H_{26}ClN_5O_5$
Exact Mass: 535.16
Mol. Wt.: 535.98

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

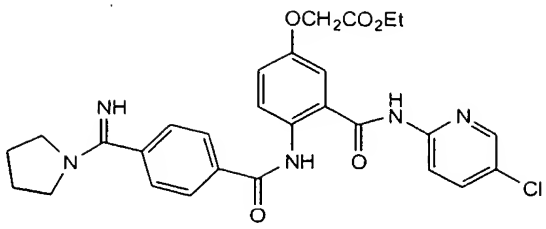
Example 244



$C_{25}H_{22}ClN_5O_5$
Exact Mass: 507.13
Mol. Wt.: 507.93

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{22}ClN_5O_5$: $(M+H)^+$: 508.1.

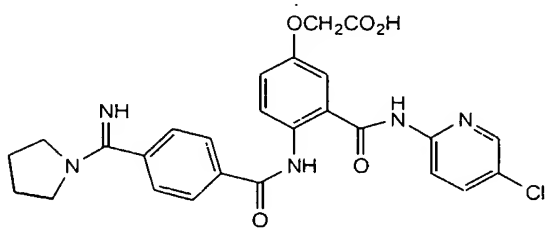
Example 245



$C_{28}H_{28}ClN_5O_5$
Exact Mass: 549.18
Mol. Wt.: 550.01

The title compound was synthesized according to the procedure described previously. MS found for $C_{28}H_{28}ClN_5O_5$: $(M+H)^+$: 550.2.

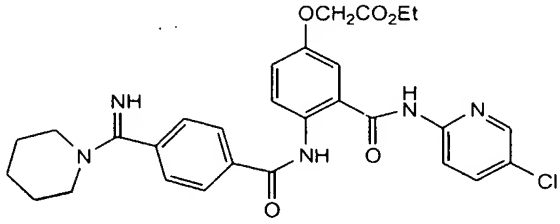
Example 246



$C_{26}H_{24}ClN_5O_5$
Exact Mass: 521.15
Mol. Wt.: 521.95

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{24}ClN_5O_5$: $(M+H)^+$: 522.1.

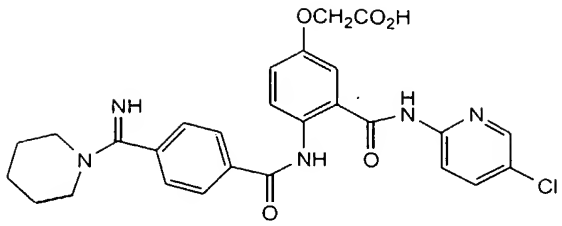
Example 247



$C_{29}H_{30}ClN_5O_5$
Exact Mass: 563.19
Mol. Wt.: 564.03

The title compound was synthesized according to the procedure described previously. MS found for $C_{29}H_{30}ClN_5O_5$: $(M+H)^+$: 564.2.

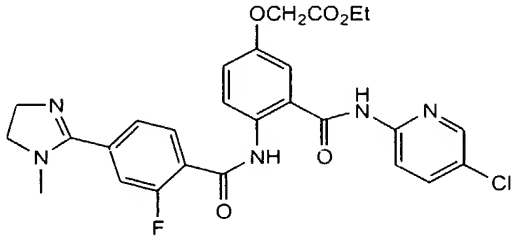
Example 248



$C_{27}H_{26}ClN_5O_5$
Exact Mass: 535.16
Mol. Wt.: 535.98

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

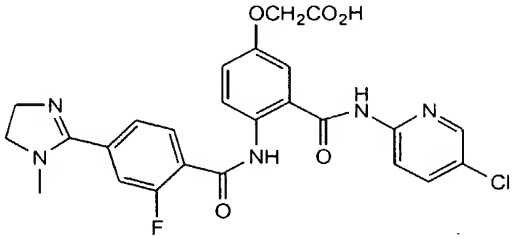
Example 249



$C_{27}H_{25}ClFN_5O_5$
Exact Mass: 553.15
Mol. Wt.: 553.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{25}ClFN_5O_5$: $(M+H)^+$: 554.2.

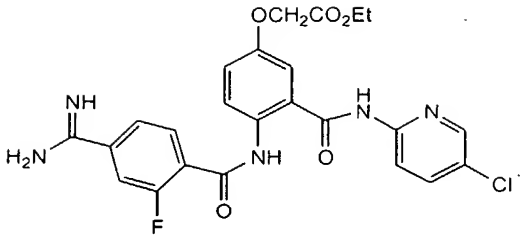
Example 250



$C_{25}H_{21}ClFN_5O_5$
Exact Mass: 525.12
Mol. Wt.: 525.92

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{21}ClFN_5O_5$: $(M+H)^+$: 526.1.

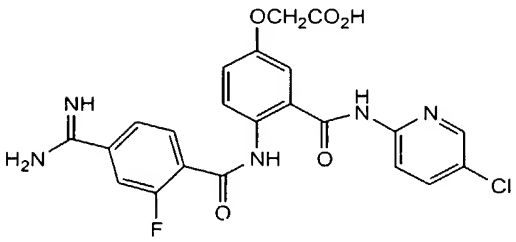
Example 251



$C_{24}H_{21}ClFN_5O_5$
Exact Mass: 513.12
Mol. Wt.: 513.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_5$: $(M+H)^+$: 514.1.

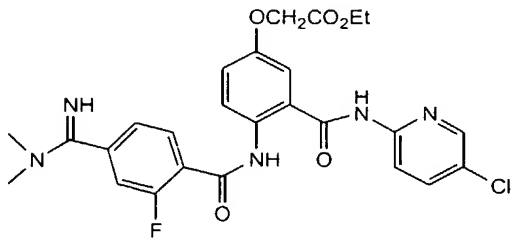
Example 252



$C_{22}H_{17}ClFN_5O_5$
Exact Mass: 485.09
Mol. Wt.: 485.85

The title compound was synthesized according to the procedure described previously. MS found for $C_{22}H_{17}ClFN_5O_5$: $(M+H)^+$: 486.

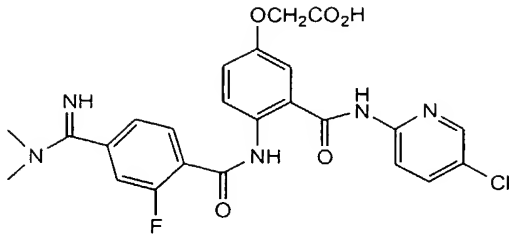
Example 253



$C_{26}H_{25}ClFN_5O_5$
Exact Mass: 541.15
Mol. Wt.: 541.96

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{25}ClFN_5O_5$: $(M+H)^+$: 542.1.

Example 254

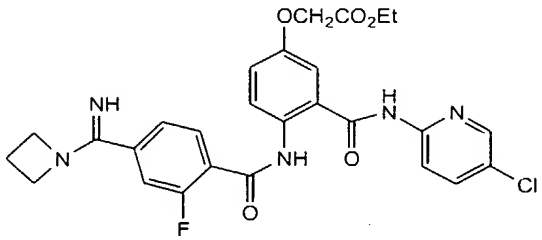


$C_{24}H_{21}ClFN_5O_5$
Exact Mass: 513.12
Mol. Wt.: 513.91

The title compound was synthesized according to the procedure described previously.

MS found for $C_{24}H_{21}ClFN_5O_5$: $(M+H)^+$: 514.1.

Example 255

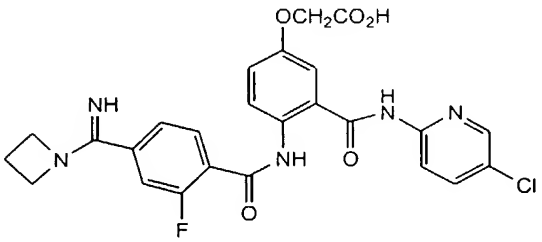


$C_{27}H_{25}ClFN_5O_5$
Exact Mass: 553.15
Mol. Wt.: 553.97

The title compound was synthesized according to the procedure described previously.

MS found for $C_{27}H_{25}ClFN_5O_5$: $(M+H)^+$: 554.1.

Example 256

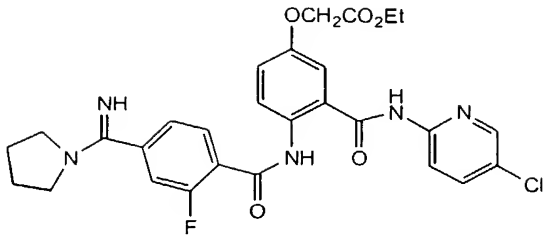


$C_{25}H_{21}ClFN_5O_5$
Exact Mass: 525.12
Mol. Wt.: 525.92

The title compound was synthesized according to the procedure described previously.

MS found for $C_{25}H_{21}ClFN_5O_5$: $(M+H)^+$: 526.1.

Example 257

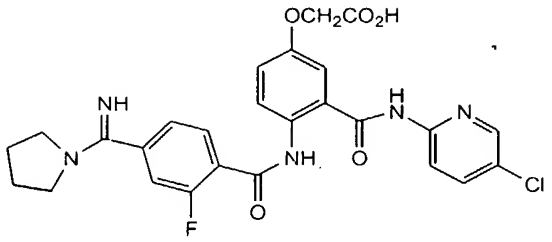


$C_{28}H_{27}ClFN_5O_5$
Exact Mass: 567.17
Mol. Wt.: 568.00

The title compound was synthesized according to the procedure described previously.

MS found for $C_{28}H_{27}ClFN_5O_5$: $(M+H)^+$: 568.1.

Example 258

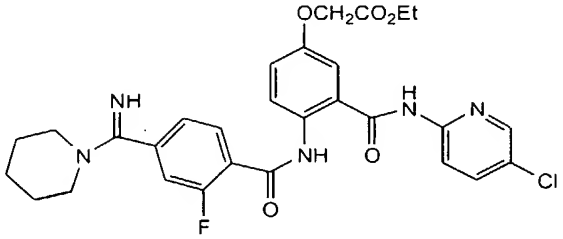


$C_{26}H_{23}ClFN_5O_5$
Exact Mass: 539.14
Mol. Wt.: 539 94

The title compound was synthesized according to the procedure described previously.

MS found for $C_{26}H_{23}ClFN_5O_5$: $(M+H)^+$: 540.1.

Example 259

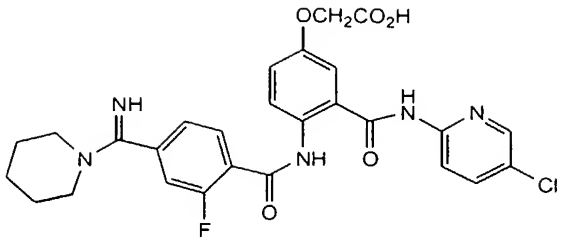


$C_{29}H_{29}ClFN_5O_5$
Exact Mass: 581.18
Mol. Wt.: 582.02

The title compound was synthesized according to the procedure described previously.

MS found for $C_{29}H_{29}ClFN_5O_5$: $(M+H)^+$: 582.2.

Example 260

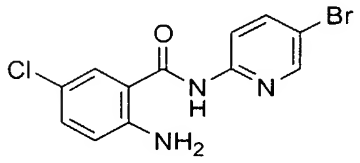


$C_{27}H_{25}ClFN_5O_5$
Exact Mass: 553.15
Mol. Wt.: 553.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{25}ClN_5O_5$: $(M+H)^+$: 554.1.

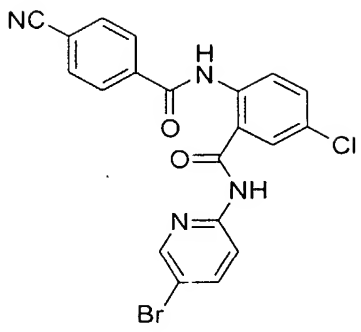
Example 261

Step 1:



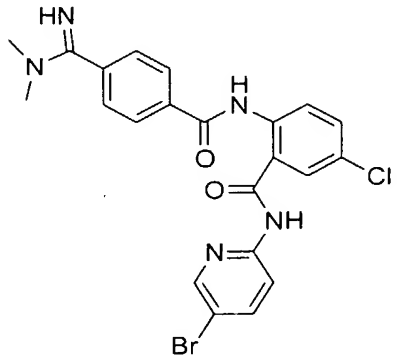
To a solution of 2-amino-5-bromopyridine (882mg, 5.1mmol) in tetrahydrofuran (5ml) was added 0.5M potassium bis(trimethylsilyl)amide in toluene (20ml, 10.1mmol) dropwise at –78 °C. After stirred for additional 0.5hr at –78 °C, the mixture was added 5-chloroisatoic anhydride (1g, 5.1mmol) at –78 °C. The mixture was warmed up to r.t gradually and stirred overnight. After concentrated, the crude was washed with saturated ammonium chloride solution and extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-bromophenyl)-N-(5-chloro(2-pyridyl))carboxamide as yellow solid (1.54g. 92%). MS found for C12H9BrClN3O M^+=327, $(M+2)^+$=329.

Step 2:



To a solution of the compound of (2-amino-5-bromophenyl)-N-(5-chloro(2-pyridyl))carboxamide (1.33g, 4.07mmol) in dichloromethane (10ml) was added 4-cyanobenzoly chloride (808mg, 4.88mmol) and pyridine (1ml, 12.21mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with a little amount of dichloromethane to give N-{4-chloro-2-[N-(5-bromo(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as yellow solid (1.36g, 73%). MS found for C20H12BrClN4O2 M^+=455, $(M+2)^+$=457.

Step 3:

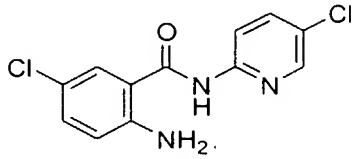


To a solution of the compound of N-{4-chloro-2-[N-(5-bromo(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1.36g, 3mmol) in anhydrous pyridine (20ml) and triethyl amine (2ml) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at r.t. overnight. After concentrated, the residue was dissolved in anhydrous acetone (20ml) and iodomethane (1.87ml,

30mmol) was added. The mixture was refluxed for 2 hrs. After concentrated, the residue was dissolved in anhydrous methanol (20ml) and a solution of 2M dimethylamine (in THF) (15ml, 30mmol) and acetic acid (10ml) in anhydrous methanol (5ml) was added. The mixture was refluxed for 2 hrs. After concentrated, the crude residue was purified by RP-HPLC to give target as white solid (750mg, 50%). MS found C22H19BrClN5O2 M^+=500, $(M+2)^+$=502.

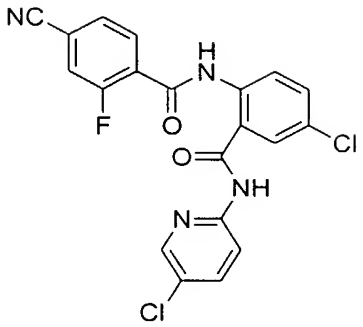
Example 262

Step 1:



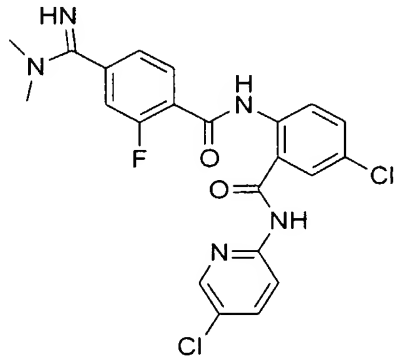
To a solution of 2-amino-5-chloropyridine (787mg, 6.1mmol) in tetrahydrofuran (5ml) was added 0.5M potassium bis(trimethylsilyl)amide in toluene (20ml, 10.1mmol) dropwise at –78 °C. After stirred for additional 0.5hr at –78 °C, the mixture was added 5-chloroisatoic anhydride (1g, 5.1mmol) at –78 °C. The mixture was warmed up to r.t gradually and stirred overnight. After concentrated, the crude was washed with saturated ammonium chloride solution and extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide as yellow solid (1.39g. 99%). MS found for C12H9Cl2N3O M^+=282, $(M+2)^+$=284.

Step 2:



A solution of 2-fluoro-4-cyanobenzoic acid (1g, 6.06mmol) in thionyl chloride (5ml) was refluxed for 2 hr. After concentration, the residue was dissolved in dichloromethane (5ml). And a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (1.2g, 4.25mmol) in dichloromethane (10ml) and pyridine (1.47ml, 18.18mmol) were added. The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with a little amount of dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(2-fluoro-4-cyanophenyl)carboxamide (2.03g, 78%). MS found for C20H11Cl2FN4O2 M^+=429, $(M+2)^+$=431.

Step 3:

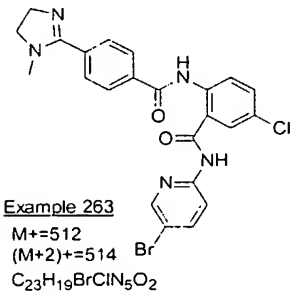


To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(2-fluoro-4-cyanophenyl)carboxamide (3g, 7mmol) in anhydrous pyridine (40ml) and triethyl amine (4ml) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at r.t. overnight. After concentrated, the

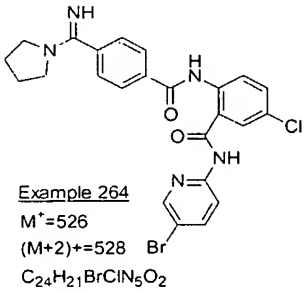
residue was dissolved in anhydrous acetone (60ml) and iodomethane (4.36ml, 70mmol) was added. The mixture was refluxed for 2 hrs. After concentrated, the residue was dissolved in anhydrous methanol (50ml) and a solution of 2M dimethylamine (in THF) (35ml, 70mmol) and acetic acid (30ml) in anhydrous methanol (15ml) was added. The mixture was refluxed for 2 hrs. After concentrated, the crude residue was purified by RP-HPLC to give target as white solid (1.7g, 50%). MS found C22H18Cl2FN5O2 M^+=474, $(M+2)^+$=476.

Examples 263-280

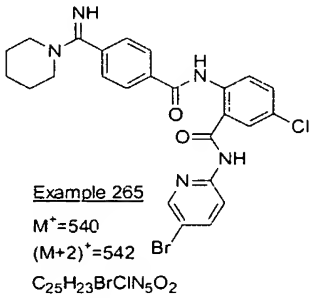
The following compounds were similarly prepared.



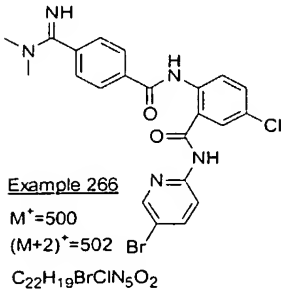
Example 263
M+=512
(M+2)+=514
$C_{23}H_{19}BrClN_5O_2$



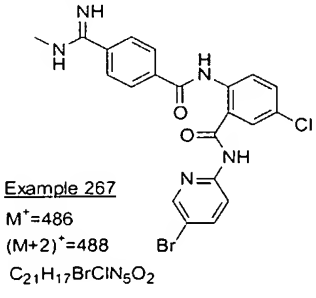
Example 264
M^+=526
(M+2)+=528
$C_{24}H_{21}BrClN_5O_2$



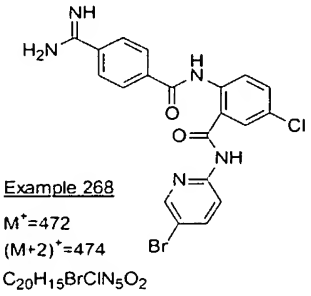
Example 265
M^+=540
$(M+2)^+$=542
$C_{25}H_{23}BrClN_5O_2$



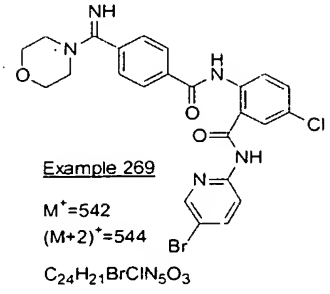
Example 266
M^+=500
$(M+2)^+$=502
$C_{22}H_{19}BrClN_5O_2$



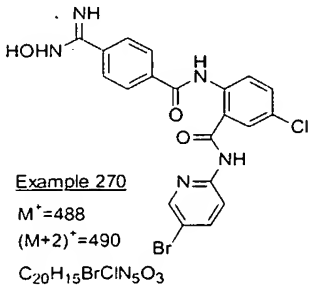
Example 267
M^+=486
$(M+2)^+$=488
$C_{21}H_{17}BrClN_5O_2$



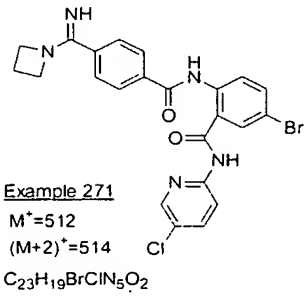
Example 268
M^+=472
$(M+2)^+$=474
$C_{20}H_{15}BrClN_5O_2$



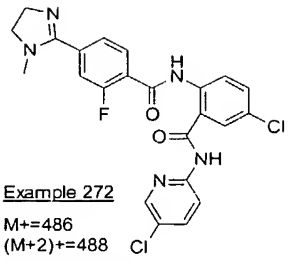
Example 269
M^+=542
$(M+2)^+$=544
$C_{24}H_{21}BrClN_5O_3$



Example 270
M^+=488
$(M+2)^+$=490
$C_{20}H_{15}BrClN_5O_3$

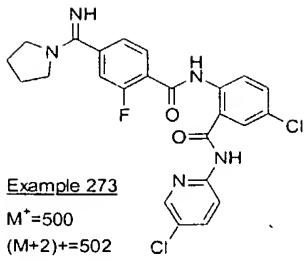


Example 271
M^+=512
$(M+2)^+$=514
$C_{23}H_{19}BrClN_5O_2$



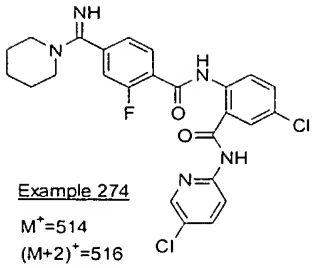
Example 272

M+=486
(M+2)+=488
$C_{23}H_{18}Cl_2FN_5O_2$



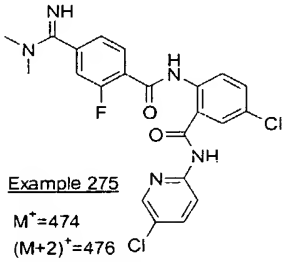
Example 273

M^+=500
$(M+2)^+$=502
$C_{24}H_{20}Cl_2FN_5O_2$



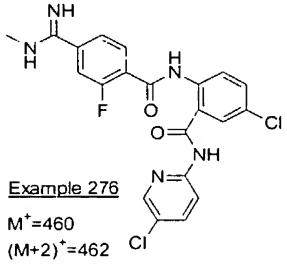
Example 274

M^+=514
$(M+2)^+$=516
$C_{25}H_{22}Cl_2FN_5O_2$



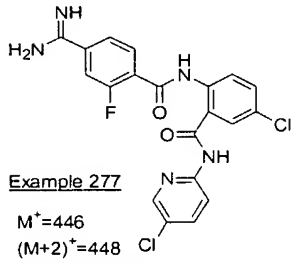
Example 275

M^+=474
$(M+2)^+$=476
$C_{22}H_{18}Cl_2FN_5O_2$



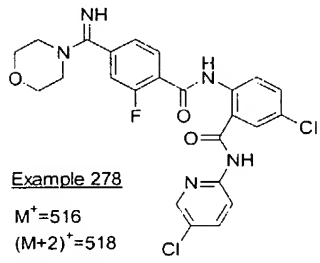
Example 276

M^+=460
$(M+2)^+$=462
$C_{21}H_{16}Cl_2FN_5O_2$



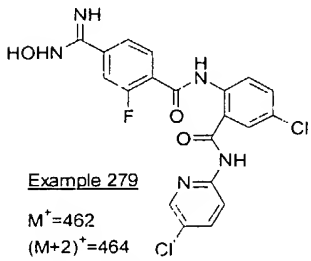
Example 277

M^+=446
$(M+2)^+$=448
$C_{20}H_{14}Cl_2FN_5O_2$



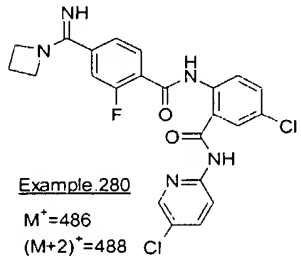
Example 278

M^+=516
$(M+2)^+$=518
$C_{24}H_{20}Cl_2FN_5O_3$



Example 279

M^+=462
$(M+2)^+$=464
$C_{20}H_{14}Cl_2FN_5O_3$

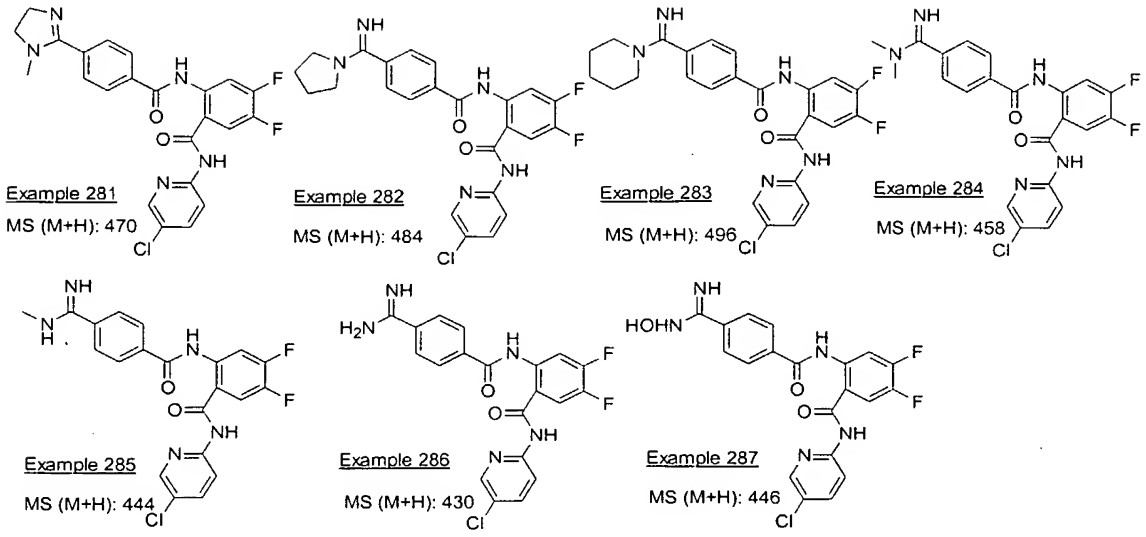


Example 280

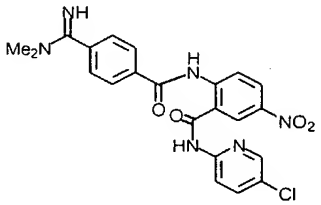
M^+=486
$(M+2)^+$=488
$C_{23}H_{18}Cl_2FN_5O_2$

Examples 281-287

The following compounds were similarly prepared.



Example 288

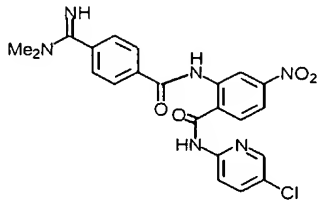


Step 1: A solution of methyl 2-amino-5-nitrobenzoate (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 1 h . The resulting mixture was quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give the desired product.

Step 2: A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added the compound obtained in step 1 (0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and purified by column chromatography to give the desired product.

Step 3: The product obtained in step 2 was subjected to standard Pinner conditions to give the title compound after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN). MS $(M+H)^+$: 467.

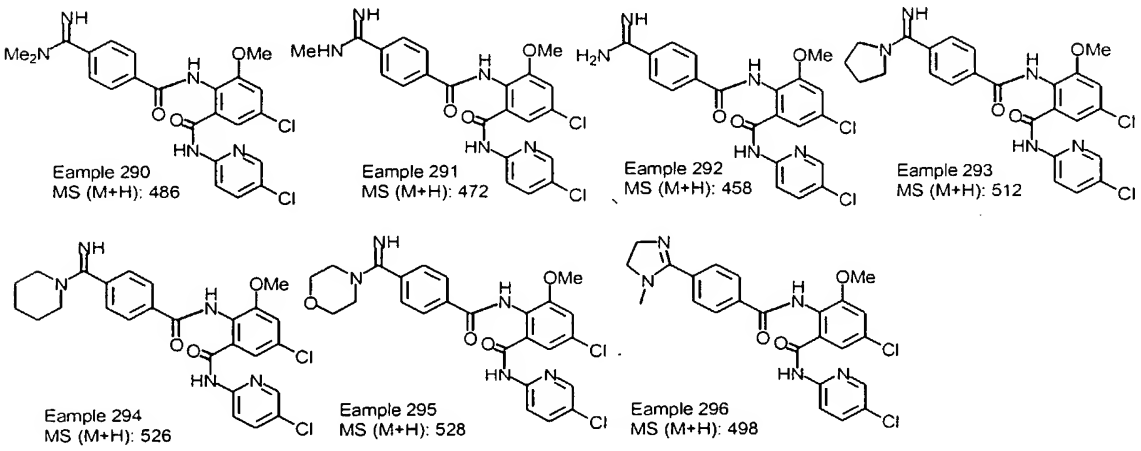
Example 289

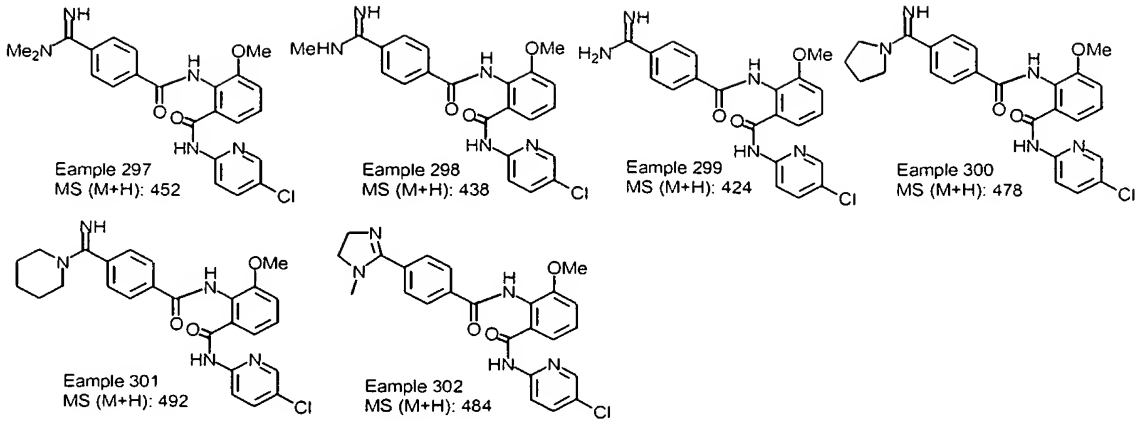


This compound was prepared according to the procedure previously described. MS $(M+H)^+$: 467.

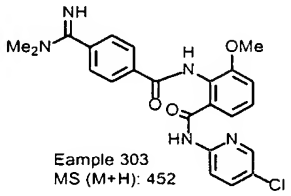
Example 290-302

The following compounds were prepared according to the procedure previously described.





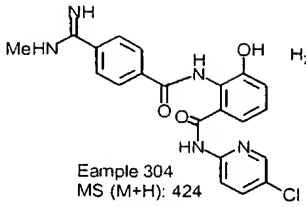
Example 303



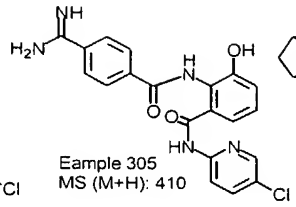
Example 297 (1 equiv) in CH_2Cl_2 was treated with BBr_3 (4 equiv) overnight, quenched with ice water. HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN) gave the title compound. MS $(M+H)^+$: 438.

Example 304-308

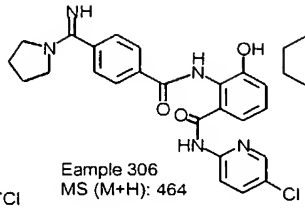
The following compounds were prepared according to the procedure previously described.



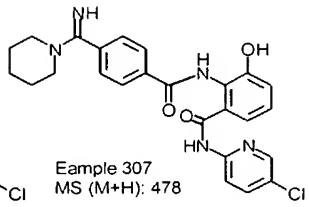
Eample 304
MS (M+H): 424



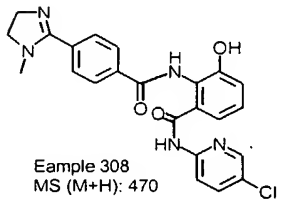
Eample 305
MS (M+H): 410



Eample 306
MS (M+H): 464



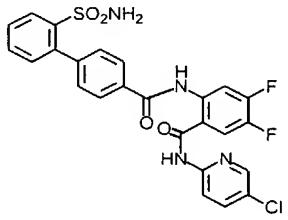
Eample 307
MS (M+H): 478



Eample 308
MS (M+H): 470

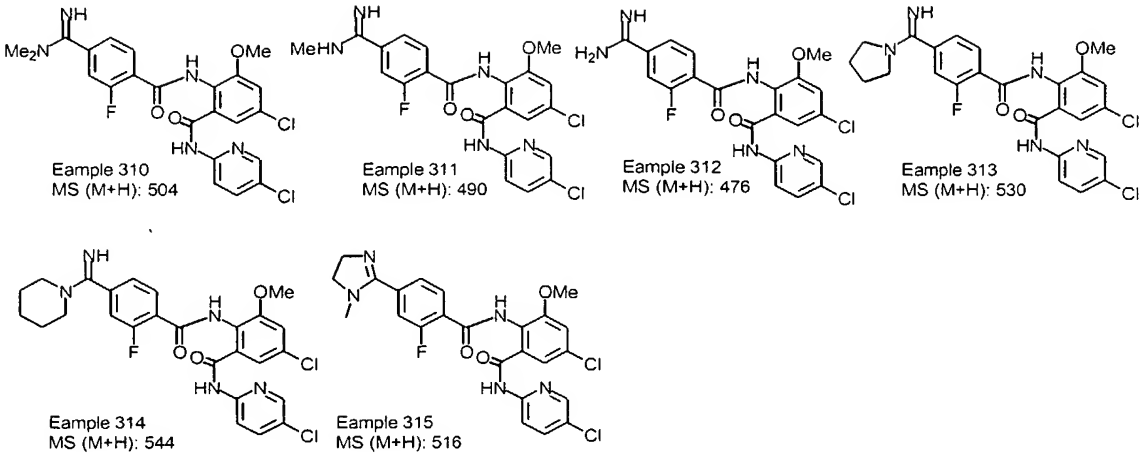
Example 309

This compound was prepared according to the procedure previously described. MS $(M+H)^+$: 543.

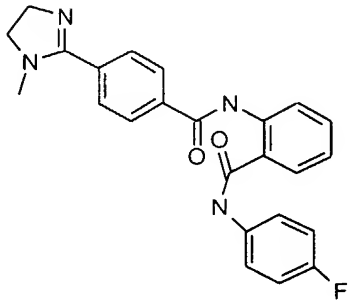


Example 310-315

The following compounds were prepared according to the procedure previously described.

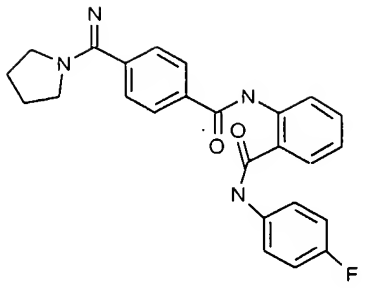


Example 316



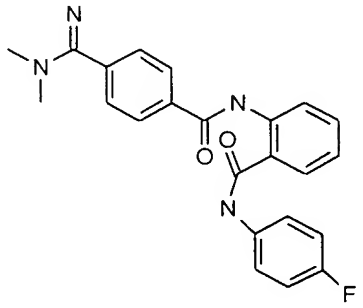
The title compound was synthesized according to the procedure described previously. ES-MS 417(M+1).

Example 317



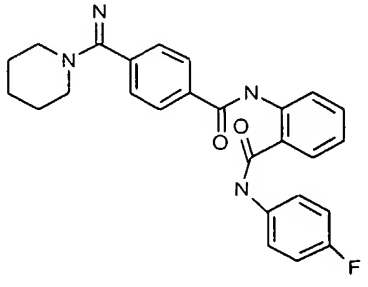
The title compound was synthesized according to the procedure described previously. ES-MS 431(M+1).

Example 318



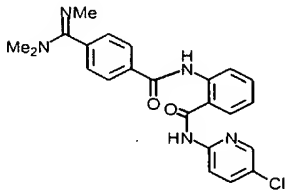
The title compound was synthesized according to the procedure described previously. ES-MS 404(M+1).

Example 319



The title compound was synthesized according to the procedure described previously. ES-MS 445(M+1).

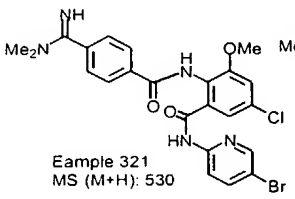
Example 320



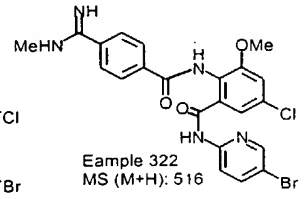
Example 53 (15 mg) was refluxed in pyridine in the presence of 0.1 mL of MeI overnight. The volatile was evaporated and the residue was purified by HPLC to give example 403. MS (M+H): 436.

Examples 321-322

The following compounds were prepared according to the procedure previously described.

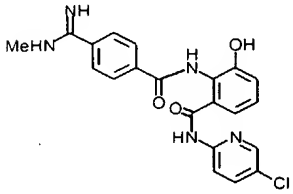


Eample 321
MS (M+H): 530



Eample 322
MS (M+H): 516

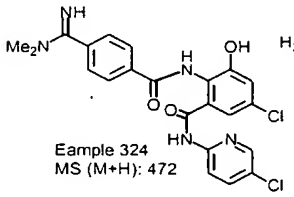
Example 323



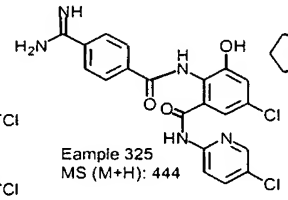
Compound 304 (20 mg) was dissolved in 10 mL of CH_2Cl_2 and was treated with 2 mL of BBr_3 (1N in CH_2Cl_2) overnight. The reaction was quenched with water and reverse phase HPLC gave the desired product. ES-MS 424 (M+H).

Example 324-336

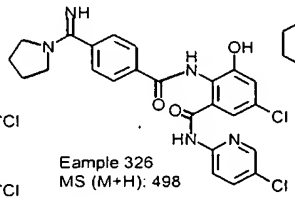
The following compounds were prepared according to the procedure previously described.



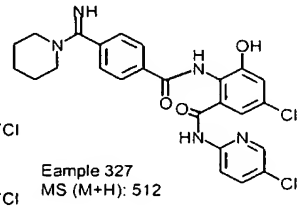
Eample 324
MS (M+H): 472



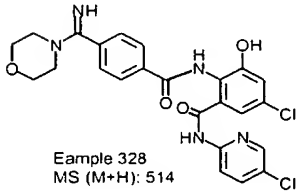
Eample 325
MS (M+H): 444



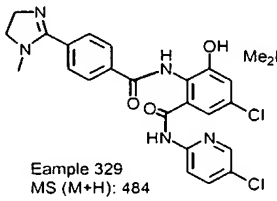
Eample 326
MS (M+H): 498



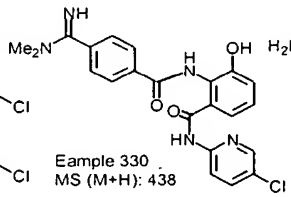
Eample 327
MS (M+H): 512



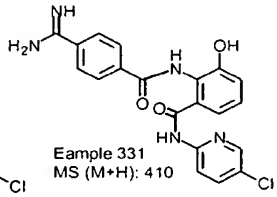
Eample 328
MS (M+H): 514



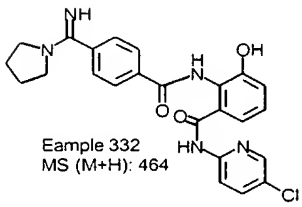
Eample 329
MS (M+H): 484



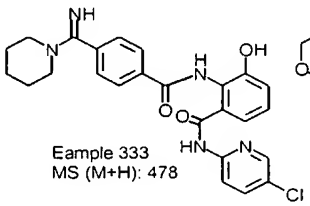
Eample 330
MS (M+H): 438



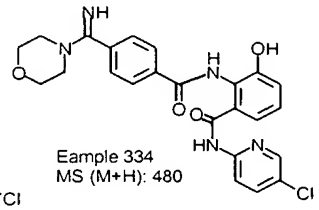
Eample 331
MS (M+H): 410



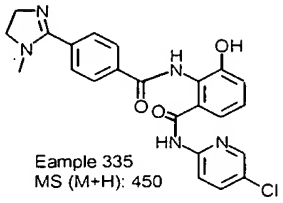
Eample 332
MS (M+H): 464



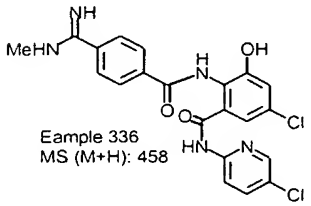
Eample 333
MS (M+H): 478



Eample 334
MS (M+H): 480



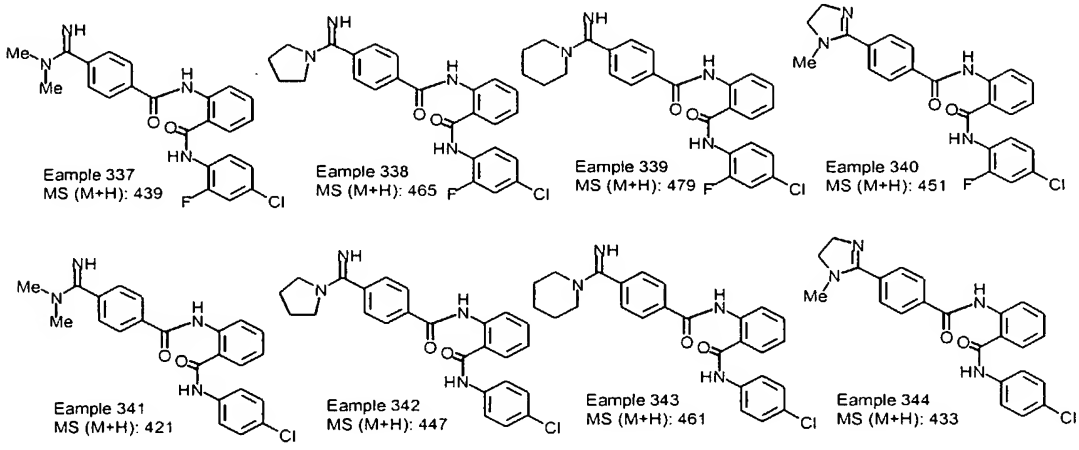
Eample 335
MS (M+H): 450



Eample 336
MS (M+H): 458

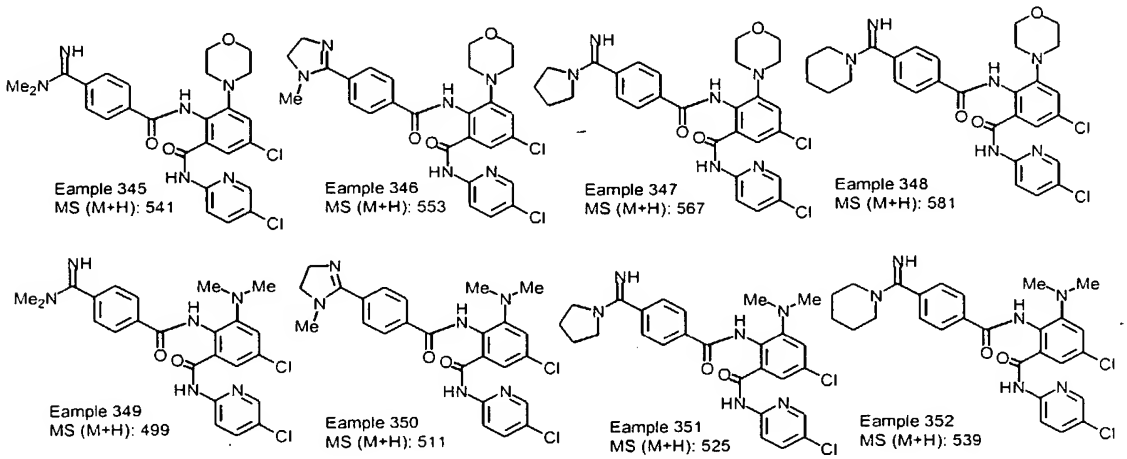
Example 337-344

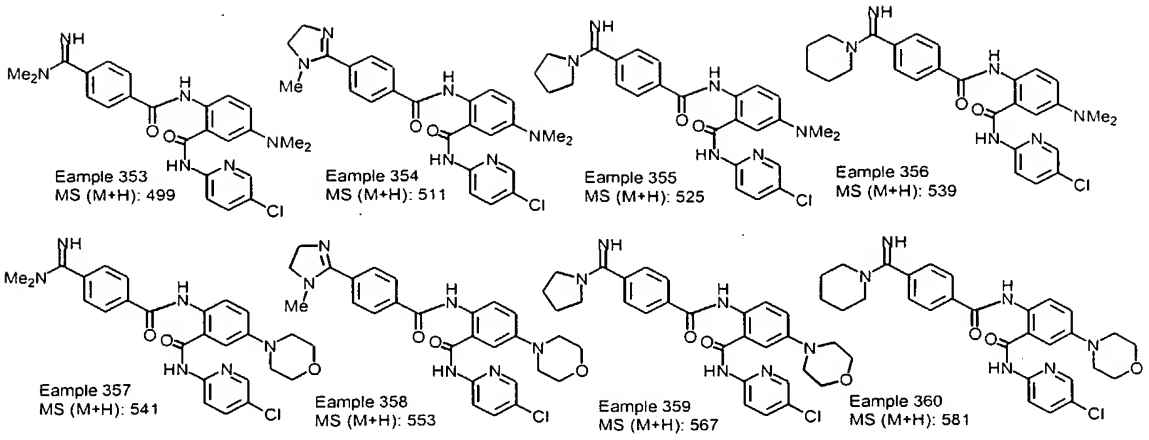
The following compounds were prepared according to the procedure previously described.



Example 345-360

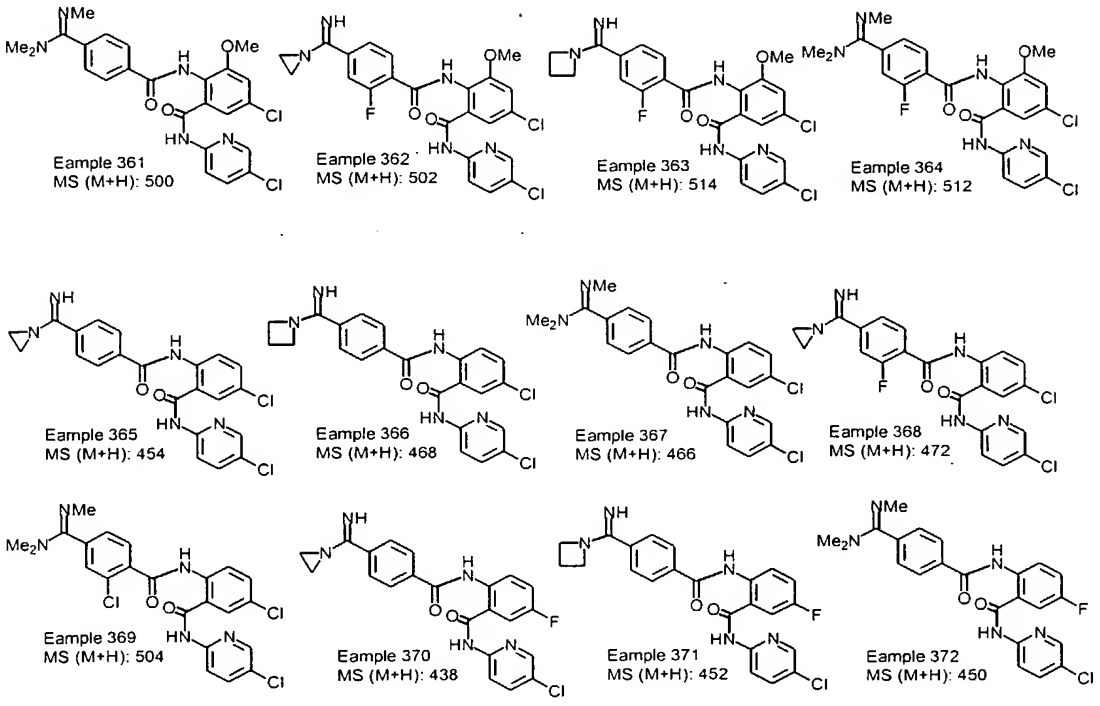
The following compounds were prepared according to the procedure previously described.

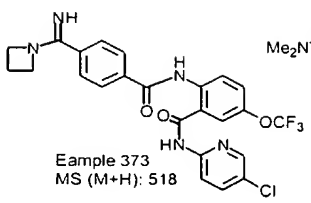


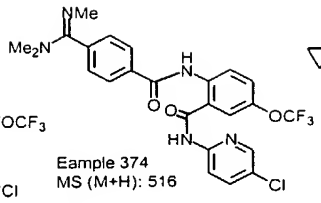


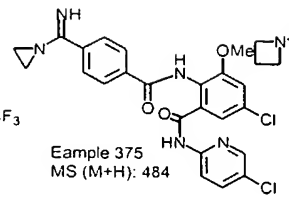
Example 361-390

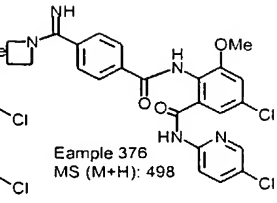
The following compounds were prepared according to the procedure previously described.

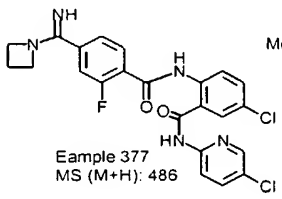


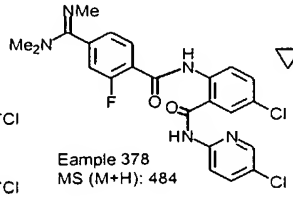

Eample 373
MS (M+H): 518

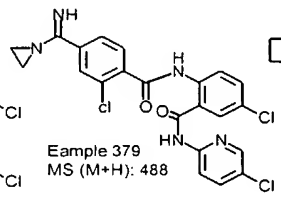

Eample 374
MS (M+H): 516

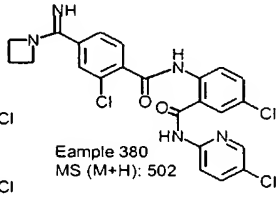

Eample 375
MS (M+H): 484

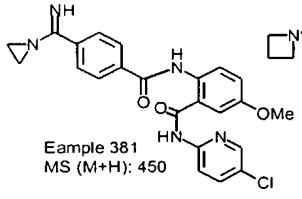

Eample 376
MS (M+H): 498

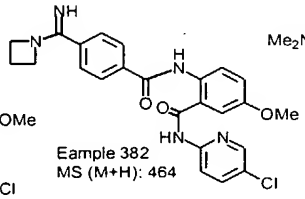

Eample 377
MS (M+H): 486

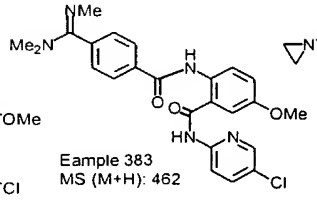

Eample 378
MS (M+H): 484

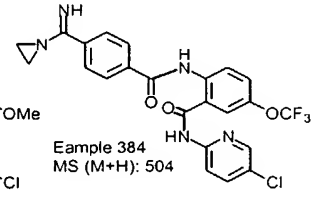

Eample 379
MS (M+H): 488

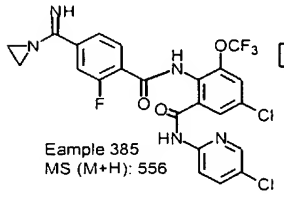

Eample 380
MS (M+H): 502

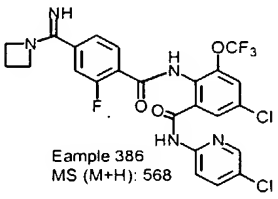

Eample 381
MS (M+H): 450

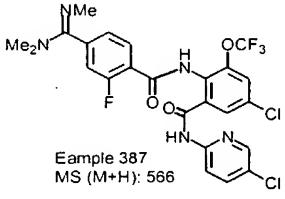

Eample 382
MS (M+H): 464

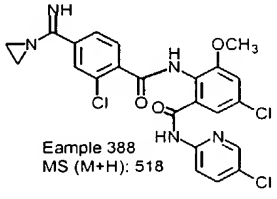

Eample 383
MS (M+H): 462

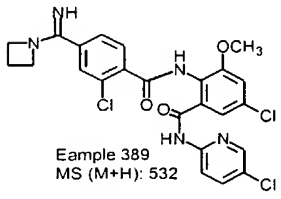

Eample 384
MS (M+H): 504

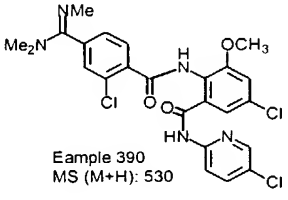

Eample 385
MS (M+H): 556


Eample 386
MS (M+H): 568


Eample 387
MS (M+H): 566


Eample 388
MS (M+H): 518

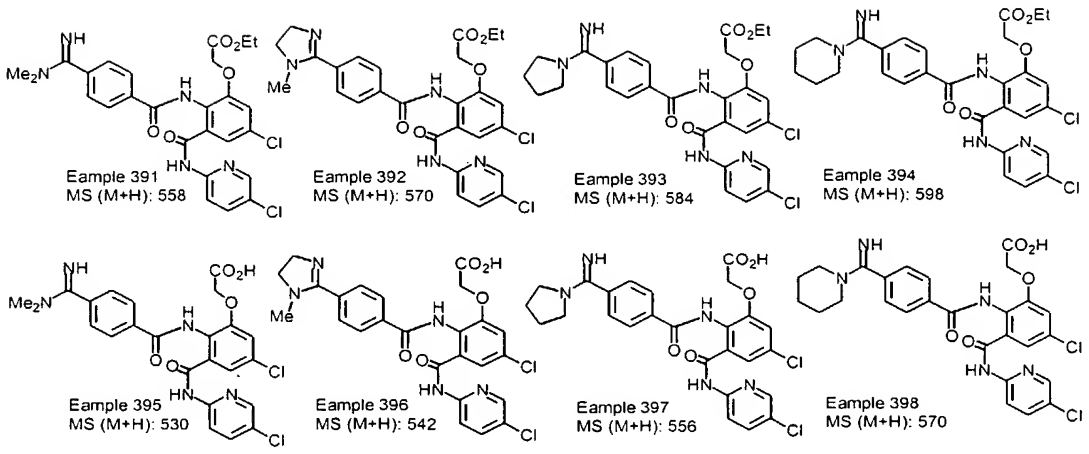

Eample 389
MS (M+H): 532


Eample 390
MS (M+H): 530

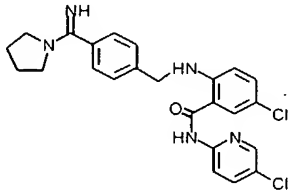
5

Example 391-398

10 The following compounds were prepared according to the procedure previously described



Example 399

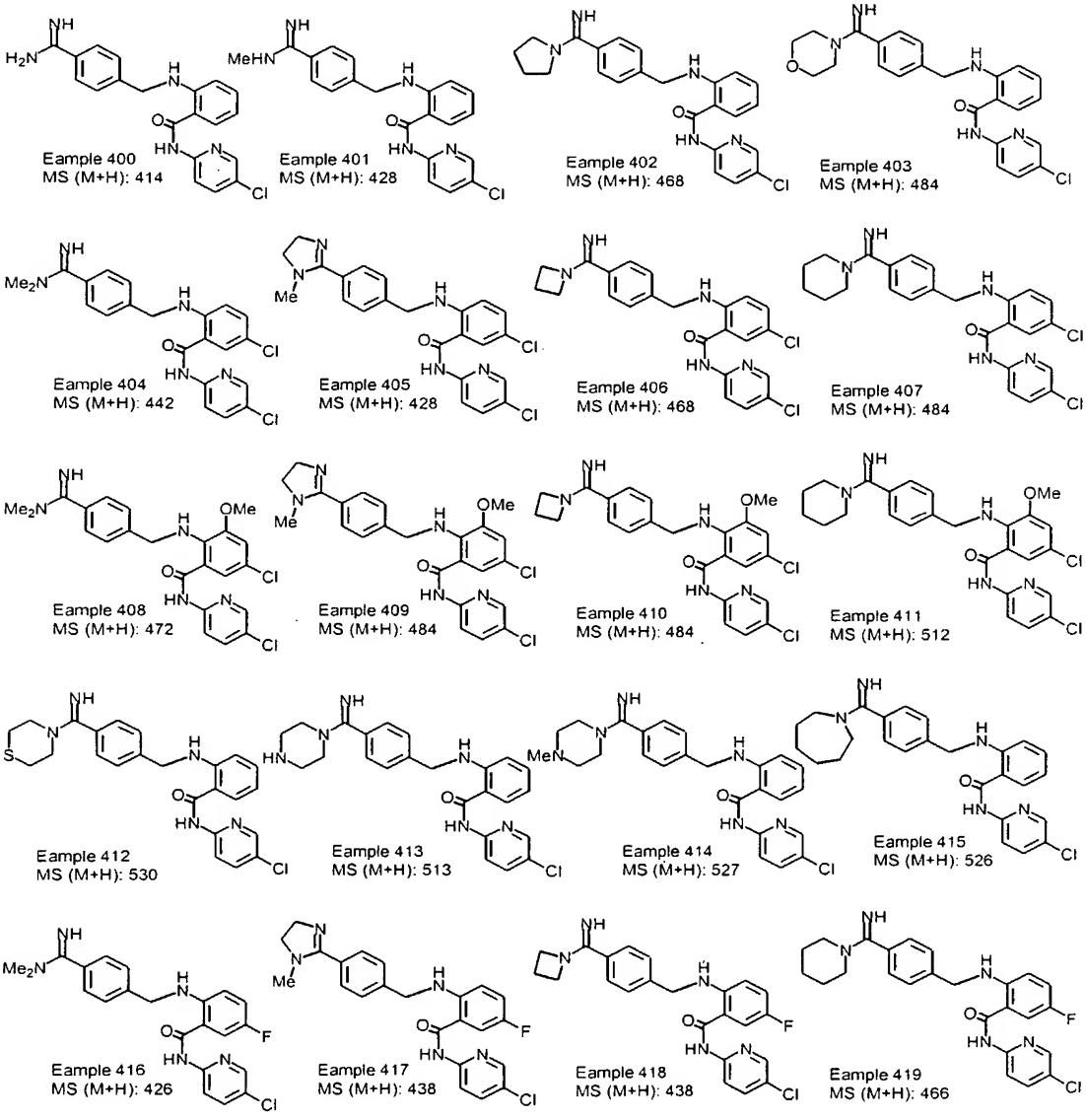


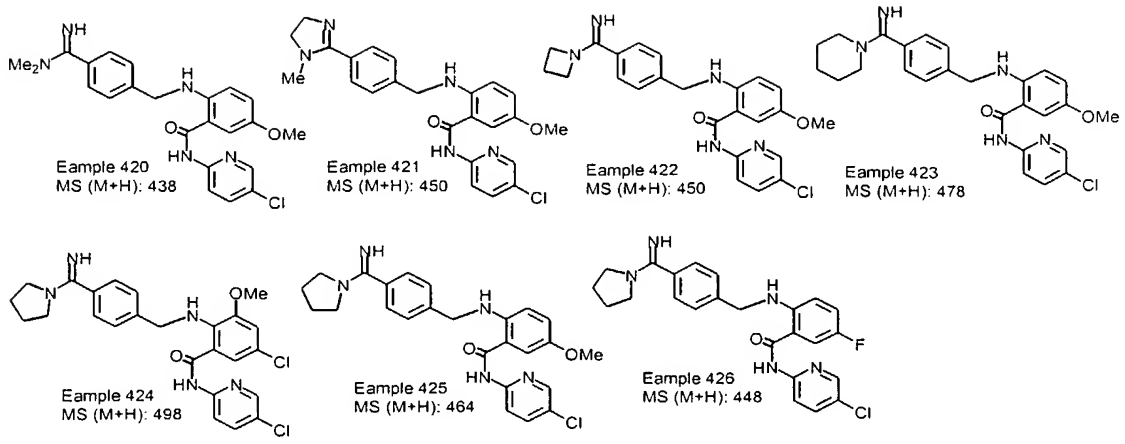
Step 1: A mixture of 4-cyanobenzaldehyde (1 equiv), 4-chloro-2-(5-chloro-2-pyridinyl)amino-carbonyl aniline (1 equiv) and glacial acetic acid (10 equiv) in CH_2Cl_2 was stirred at rt for 30 min. $NaBH(OAc)_3$ (3 equiv) was added at once and the mixture was stirred overnight. The reaction was quenched with water and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product.

Step 2: A solution of the compound obtained in step 1 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 468.

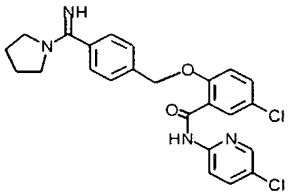
Examples 400-426

The following compounds were prepared according to the procedure previously described.





Example 427



Step 1: A mixture of 4-cyanobenzyl bromide (1 equiv), methyl 2-hydroxybenzoate (1 equiv) and cesium carbonate (10 equiv) in DMF was stirred at rt overnight. The mixture was then diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

Step 2: A solution of the compound obtained in step 1 (1 equiv) in MeOH was treated with 1N LiOH (2.2 equiv) for 1h. After removal of methanol and acidifying with 1N HCl to PH ~1, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and evaporated to give the product.

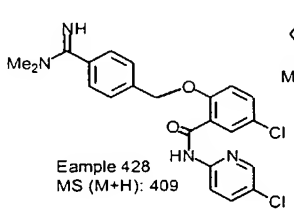
Step 3: A solution of the compound obtained in step 2 (1 equiv) in dichloromethane was treated with oxalyl chloride (3 equiv) and 2 drops of DMF at rt for 3 h. The volatile was evaporated and the residue was redissolved in methylenechloride. To the solution was added 2-amino-5-chloropyridine (1 equiv) and pyridine (5 equiv). The

mixture was stirred at rt for 2h, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

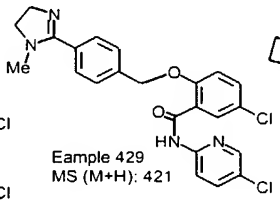
Step 2: A solution of the compound obtained in step 3 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 435.

Examples 428-431

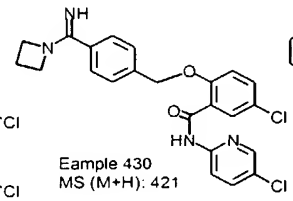
The following compounds were similarly prepared.



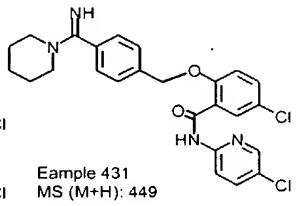
Eample 428
MS (M+H): 409



Eample 429
MS (M+H): 421

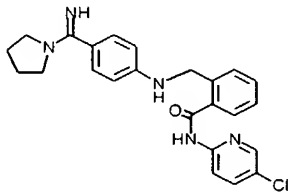


Eample 430
MS (M+H): 421



Eample 431
MS (M+H): 449

Example 432



Step 1: A solution of 2-carboxybenzaldehyde (1 equiv) in dichloromethane was treated with oxalyl chloride (3 equiv) and 2 drops of DMF at rt for 3 h. The volatile was evaporated and the residue was redissolved in methylenechloride. To the solution was added 2-amino-5-chloropyridine (1 equiv) and pyridine (5 equiv). The mixture

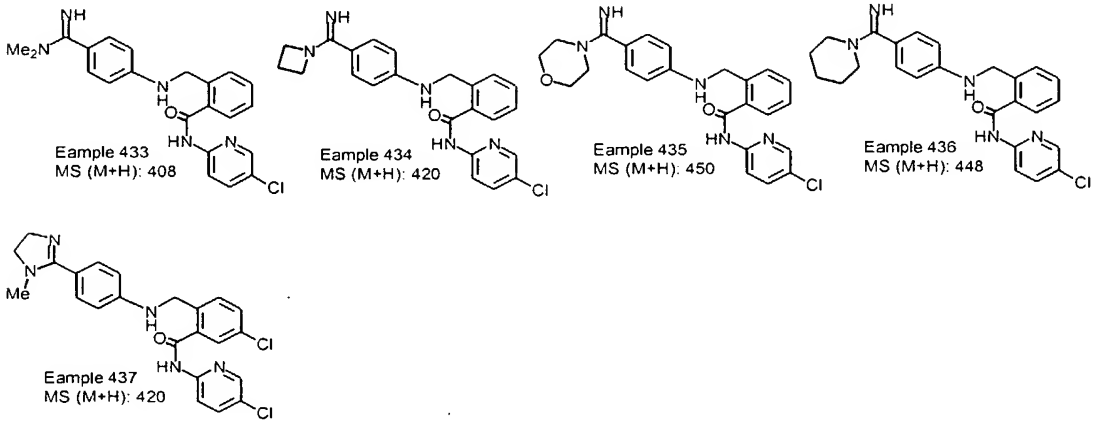
was stirred at rt for 2h, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

Step 2: A mixture of the compound obtained in step 1 (1 equiv), 4-cyanoaniline (1 equiv) and glacial acetic acid (10 equiv) in CH_2Cl_2 was stirred at rt for 30 min. $NaBH(OAc)_3$ (3 equiv) was added at once and the mixture was stirred overnight. The reaction was quenched with water and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product.

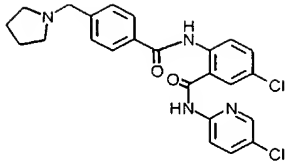
Step 3: A solution of the compound obtained in step 2 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 434.

Examples 433-437

The following compounds were similarly prepared.



Example 438

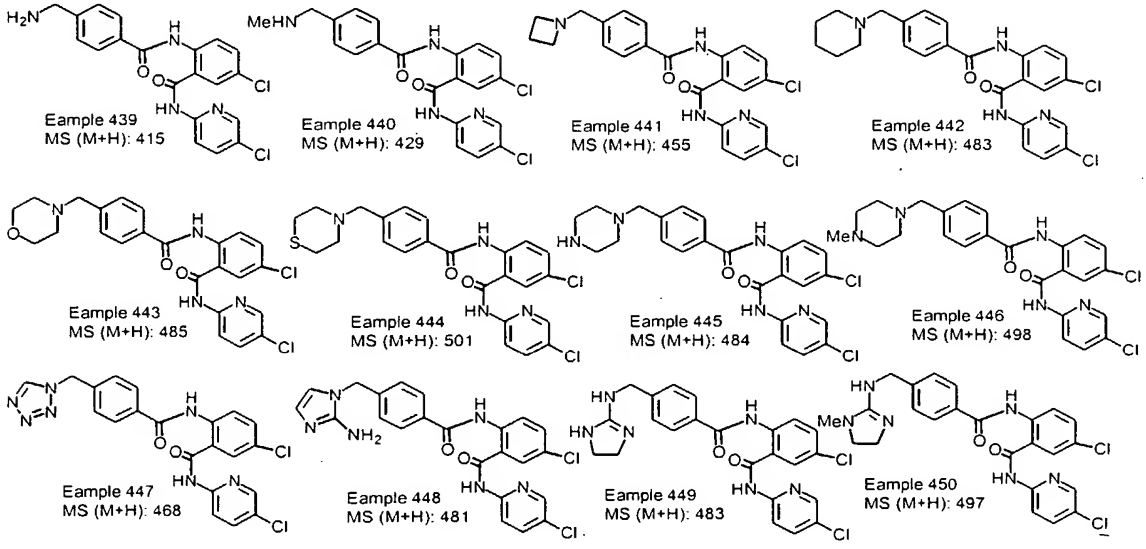


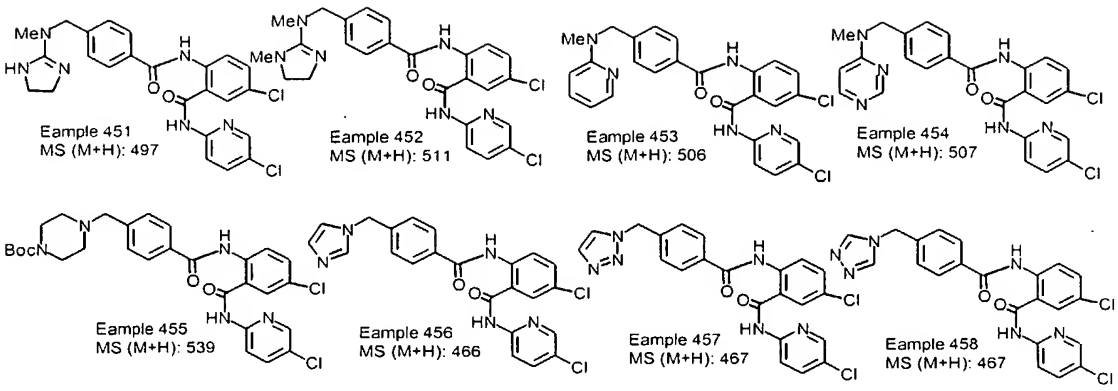
Step 1: A mixture of 4-chloromethylbemzoyl chloride (1 equiv), 4-chloro-2-(5-chloro-2-pyridinyl)amino-carbonyl aniline (1 equiv) and pyridine (5 equiv) in CH_2Cl_2 was stirred at reflux for 4 h. The reaction was cooled to rt and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product (~20% yield).

Step 2: A solution of the compound obtained in step 1 (15 mg) in DMF (1 mL) was treated with pyrrolidine (1 mL) at rt overnight. After removing the volatile, the crude residue was purified by RP-HPLC to give the target. MS (M+H) 469.

Example 439-458

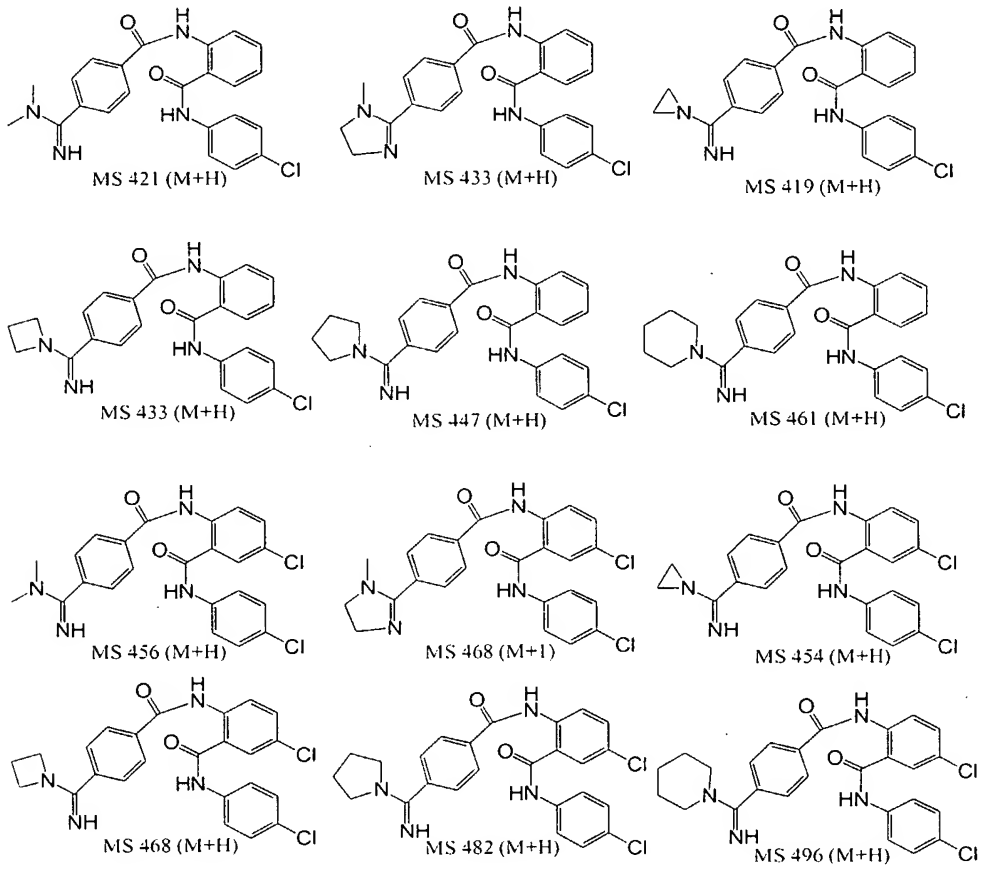
The following compounds were prepared according to the procedure previously described.

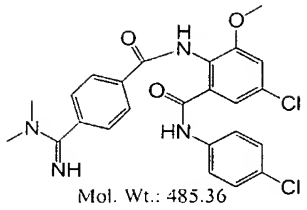


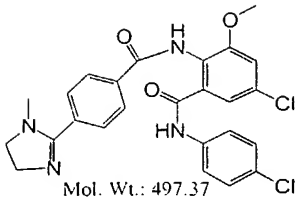


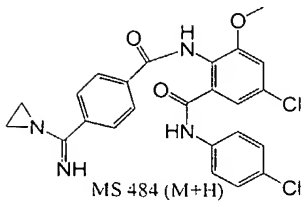
Example 459-494

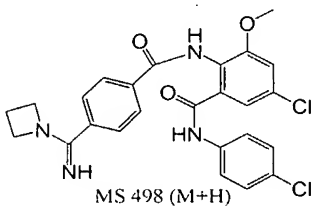
The following compounds were prepared according to the procedure previously described.

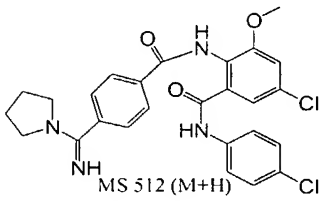


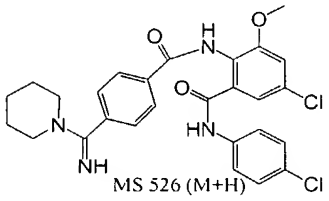

Mol. Wt.: 485.36

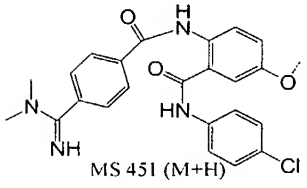

Mol. Wt.: 497.37

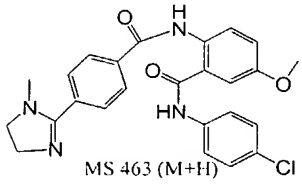

MS 484 (M+H)

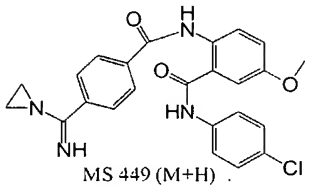

MS 498 (M+H)

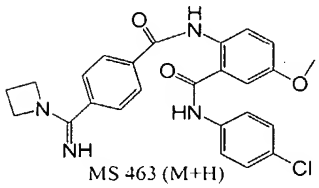

MS 512 (M+H)

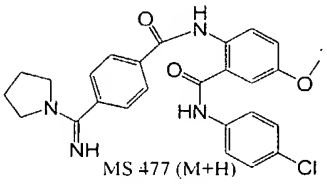

MS 526 (M+H)

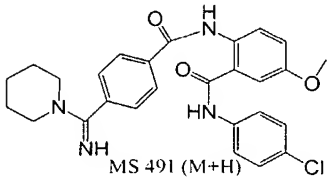

MS 451 (M+H)

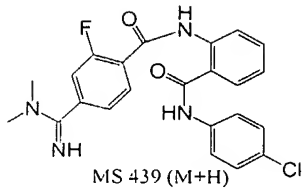

MS 463 (M+H)

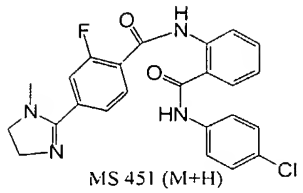

MS 449 (M+H)

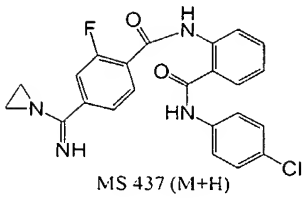

MS 463 (M+H)

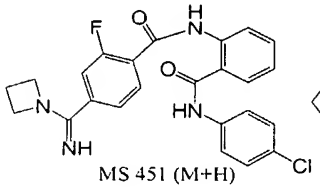

MS 477 (M+H)

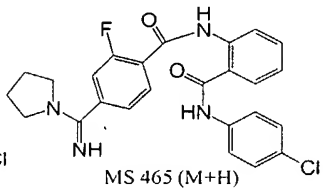

MS 491 (M+H)

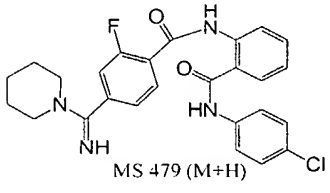

MS 439 (M+H)

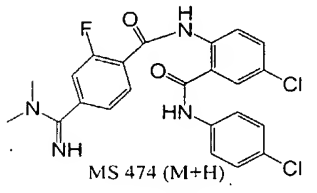

MS 451 (M+H)

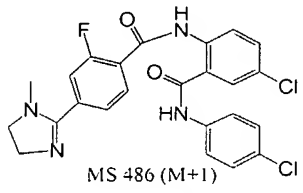

MS 437 (M+H)

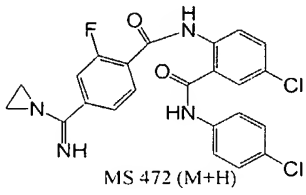

MS 451 (M+H)

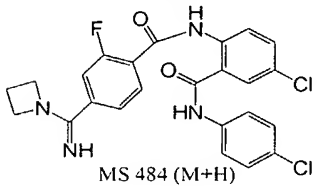

MS 465 (M+H)

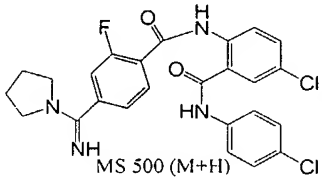

MS 479 (M+H)

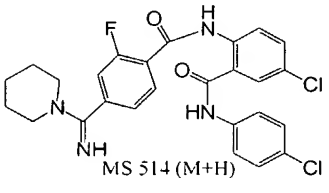

MS 474 (M+H)


MS 486 (M+1)


MS 472 (M+H)

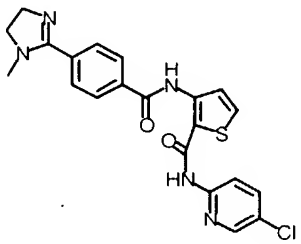

MS 484 (M+H)


MS 500 (M+H)


MS 514 (M+H)

Example 495

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



Preparation of methyl 3-[(4-cyanophenyl)carbonylamino]thiophene-2-carboxylate

A mixture of 4-cyanobenzoyl chloride (1.0500g, 6.4 mmol), methyl 3-aminothiophenecarboxylate (1.0000g, 6.4 mmol), and triethylamine (1 mL, 7.0 mmol)

in dichloromethane was stirred at room temperature for 18 hours. The mixture was poured into a separatory funnel and washed by 1 N HCl. The organic layers were combined, dried over MgSO4, concentrated in *vacuo*, and chromatographed through a silica gel column to give the title compound 1.6588 g (91%). ES-MS 287 (M+1).

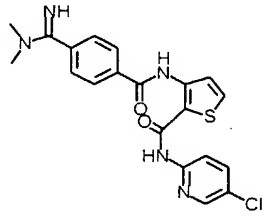
Preparation of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}(4-cyanophenyl)carboxamide

A portion of 2-amino-5-chloropyridine (68.6 mg, 0.5 mmol) was treated with AlMe3 (0.8 mL, 1.6 mmol), followed by adding the product from step A (160 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 hours. The excess of AlMe3 was killed by 1N HCl solution. The organic layers were combined, dried over MgSO4, concentrated in *vacuo*, and chromatographed through a silica gel column to give the title compound 0.1528 g (80%). ES-MS 383 (M+1).

A mixture of the product from step B (0.1528 g, 0.4 mmol) and EtOH saturated with HCl was stirred at room temperature for 18 hours. The solvent was removed by a rotovap. The crude oil was treated with 2 mL N-methylethylenediamine for 2 hours until the reaction was complete. Prep HPLC was used to purity the final product. It gave 0.1537 g (88%). ES-MS 440(M+1).

Example 496

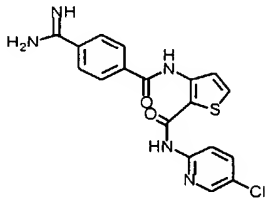
{4-[(dimethylamino)iminomethyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 428 (M+1).

Example 497

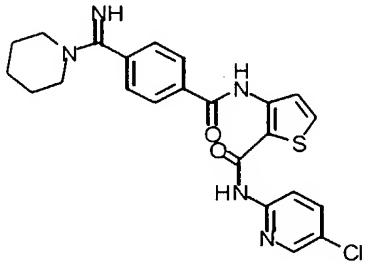
4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine



The title compound was obtained according to the procedure previously described. ES-MS 400(M+1).

Example 498

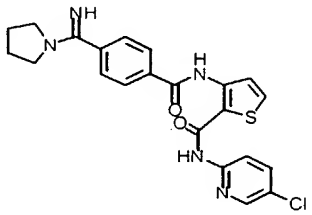
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)-phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 468(M+1).

Example 499

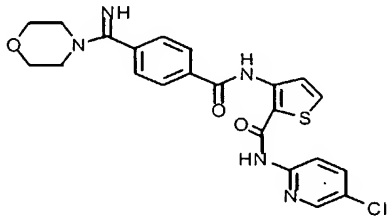
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)-phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 454(M+1).

Example 500

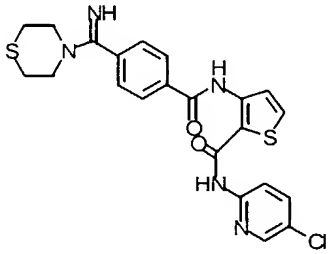
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 470(M+1).

Example 501

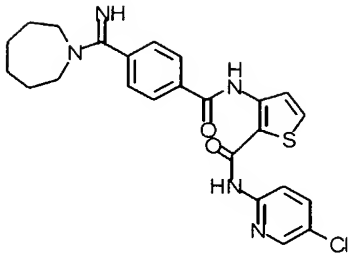
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 486(M+1).

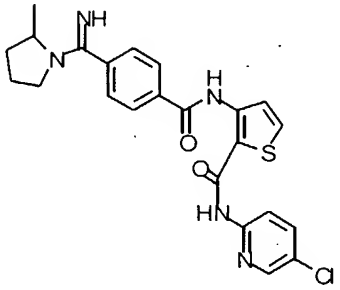
Example 502

[4-(azaperhydroepinyliminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 482(M+1).

Example 503

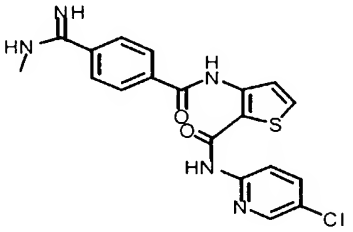


N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(2-methylpyrrolidinyl)methyl]phenyl}carboxamide

The title compound was obtained according to the procedure previously described. ES-MS 468(M+1).

Example 504

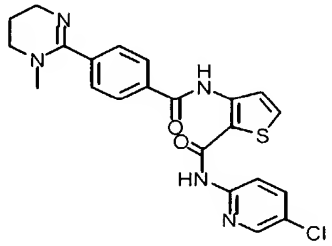
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(methylamino)methyl]-phenyl}carboxamide



The title compound was obtained according to the procedure previously described.

Example 505

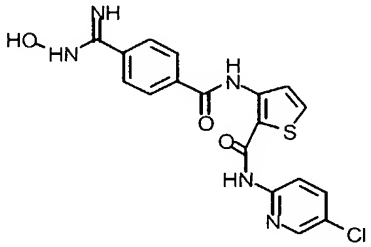
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(3-methyl(3,4,5,6-tetrahydropyrimidin-2-yl))phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 414(M+1).

Example 506

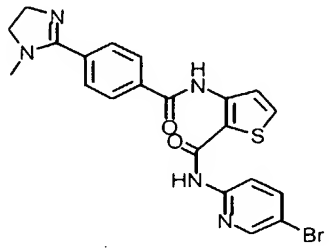
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-((hydroxyamino)iminomethyl)-phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 416(M+1).

Example 507

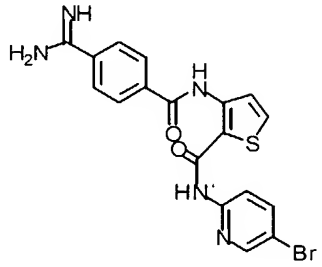
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 484(M+1).

Example 508

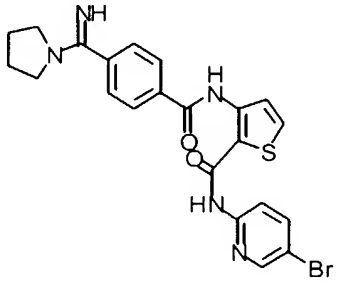
4-(N-{2-[N-(5-bromo-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine



The title compound was obtained according to the procedure previously described. ES-MS 444(M+1).

Example 509

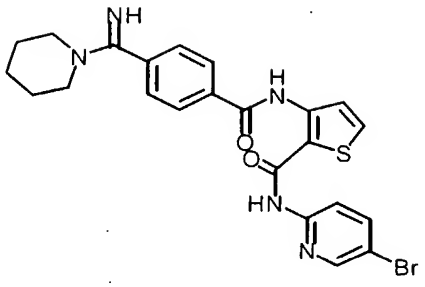
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 494(M+1).

Example 510

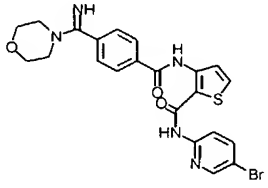
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 512(M+1).

Example 511

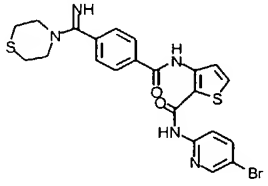
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 514(M+1).

Example 512

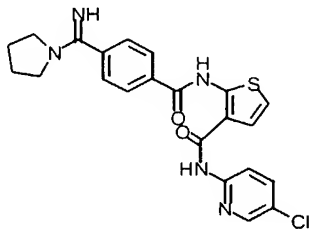
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 530(M+1).

Example 513

N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide

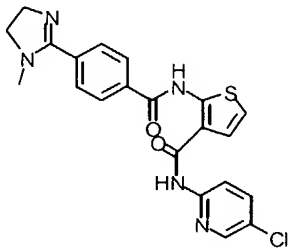


The title compound was obtained according to the procedure previously described.

ES-MS 454(M+1).

Example 514

N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide

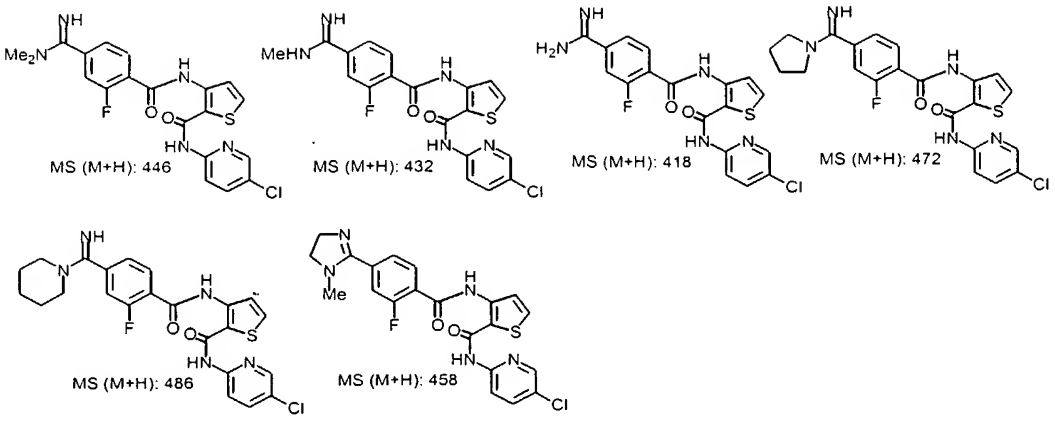


The title compound was obtained according to the procedure previously described.

ES-MS 440(M+1).

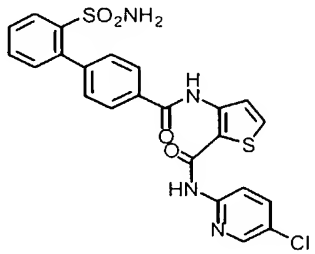
Examples 515-520

The following examples are prepared according to the procedure previously described.



Example 521

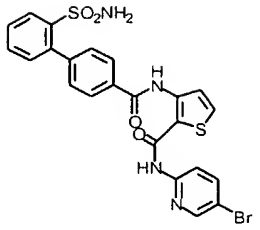
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



A solution of 4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)benzoyl chloride (1 equiv), 3-amino-2-(4-chloro-2-pyridinyl)aminocarbonyl thiophene (1 equiv), pyridine (5 equiv) in dichloromethane was stirred at rt overnight. The mixture was diluted with dichloromethane, washed with water, dried over Na2SO4, filtered and evaporated. The residue was refluxed with 1 mL of TFA for 2h. After evaporation, reverse phase HPLC gave the title product. ES-MS 513(M+1).

Example 522

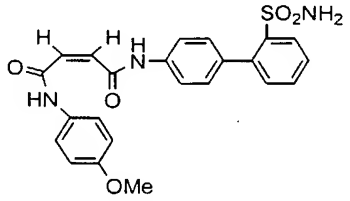
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 556(M+1).

Example 523

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)-maleamic amide.

To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M + H).

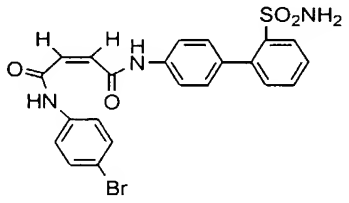
B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was

allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M + H) and 474 (M + Na). ^{1}H NMR (CDCl3) δ 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz), 7.60 – 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 524

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester.

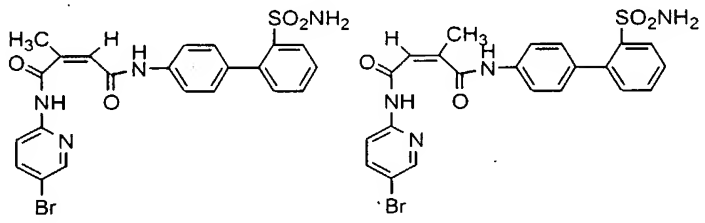
To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M + H - ^{t}Bu) and 439 (M + Na).

B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH2Cl2 (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M + H), 522 and 524 (M + Na). ^{1}H NMR (CD3OD) δ 8.09 (d, 1H, J = 8 Hz), 7.68 (d, 2H, J = 8 Hz), 7.64 – 7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 525 and 526

Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl] phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.



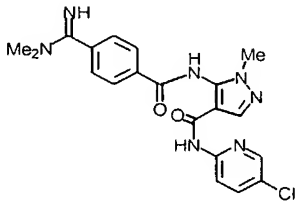
A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M + H).

B. Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl] phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH2Cl2 (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1 : 5. MS 515 and 517 (M + H), 537 and 539 (M + Na).

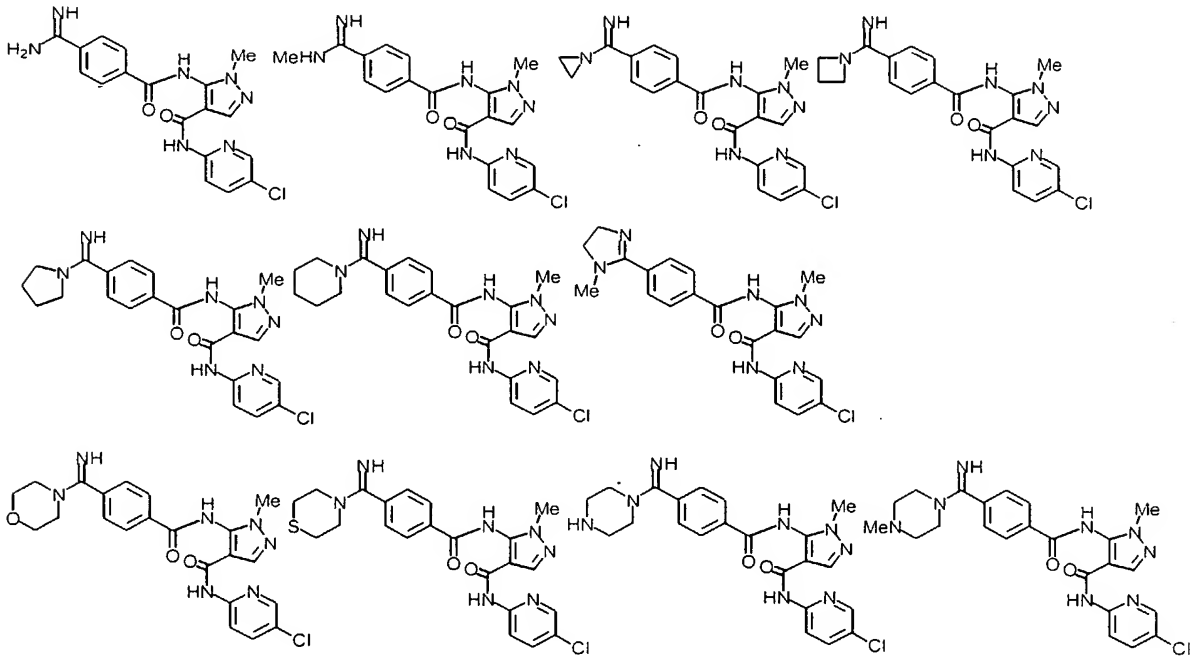
Example 527



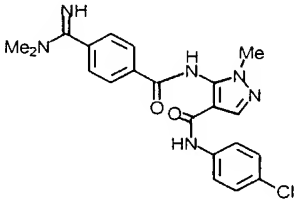
A solution of 3-amino-4-[(5-chloro-2-pyridinyl)aminocarbonyl] pyrazole (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 30 min . The resulting mixture was quenched by slow addition of water, and extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation, the residue was trituated with a small amount of CH_2Cl_2 and EtOAc. The solid on the glass wall was then subjected to standard Pinner conditions to give desired product. MS $(M+H)^+$: 426.

Examples 528-538

The following examples were prepared according to the procedure previously described.



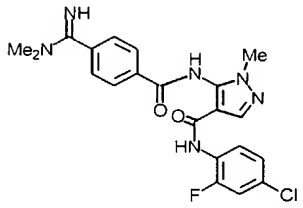
Example 539



Step 1: A solution of 3-amino-4-ethoxycarbonyl-pyrazole (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 1 h. The resulting mixture was quenched by slow addition of water, extracted with CH_2Cl_2, dried over $MgSO_4$, and purified by column chromatography to give the desired product.

Step 2: The compound obtained in step 1 (1 equiv) in DMF was treated with NaSMe (10 equiv) at 65 °C overnight. The resulting mixture was quenched by slow addition of water, and acidified with 1 N HCl, extracted with EtOAc, and dried over $MgSO_4$. The acid was reflux in excess $SOCl_2$ for 2 h. The volatile was removed on rotovap, and the residue was redissolved in pyridine, refluxed overnight in the prsence of DMAP (1 equiv) and 4-chloroaniline (10 equiv). The resulting mixture was quenched by slow addition of water, and extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation, the residue was trituated with a small amount of CH_2Cl_2 and EtOAc. The solid on the glass wall was then subjected to standard Pinner conditions to give desired product. MS $(M+H)^+$: 425.

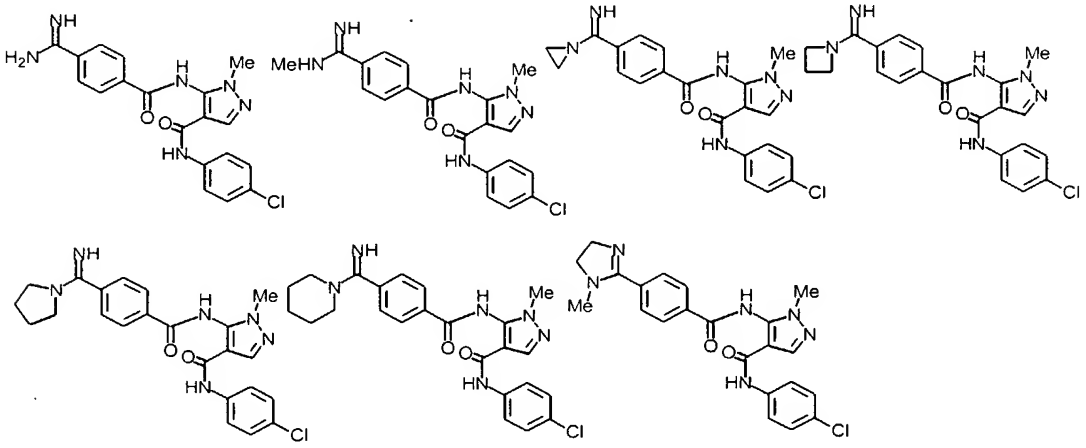
Example 540

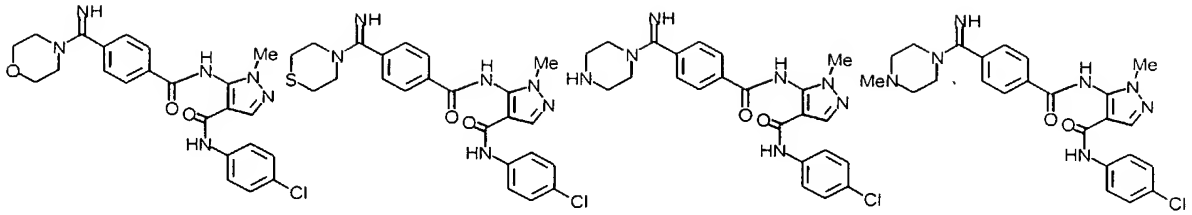


Similarly prepared as Example 350. MS $(M+H)^+$: 443.

Examples 541-551

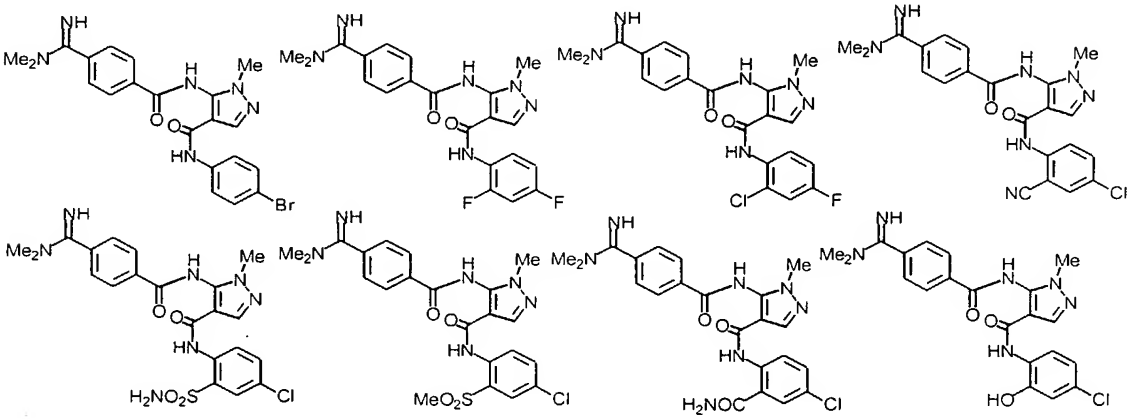
The following examples were prepared according to the procedure previously described.



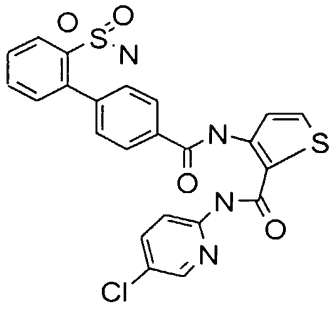


Examples 552-559

The following examples were prepared according to the procedure previously described.



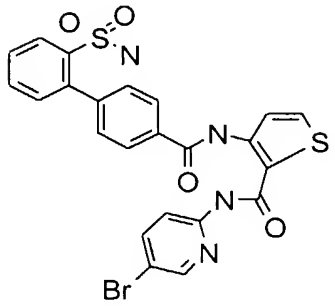
Example 560



The title compound was synthesized according to the procedure described previously.

ES-MS 514(M+1).

Example 561

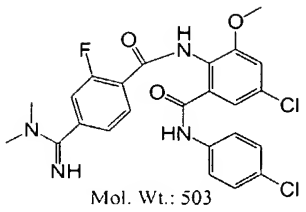


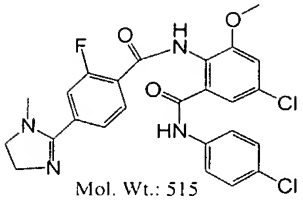
The title compound was synthesized according to the procedure described previously.

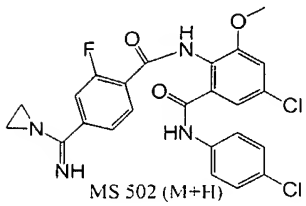
ES-MS 558(M+1).

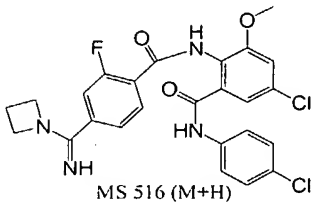
Example 562-585

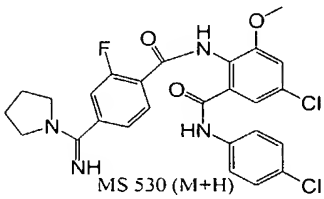
The following compounds were prepared according to the procedure previously described.

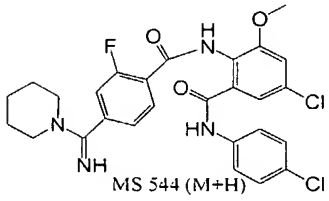

Mol. Wt.: 503

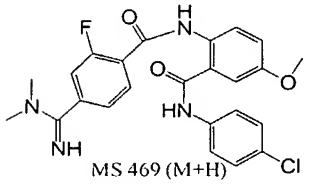

Mol. Wt.: 515

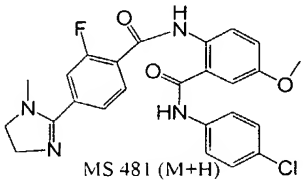

MS 502 (M+H)

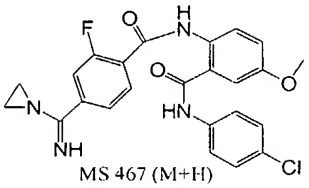

MS 516 (M+H)

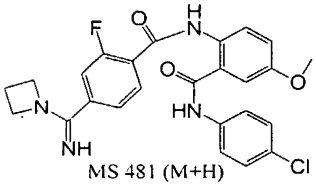

MS 530 (M+H)

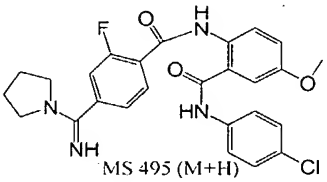

MS 544 (M+H)

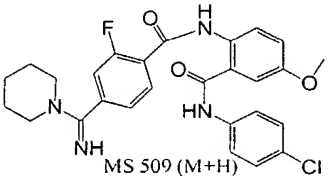

MS 469 (M+H)

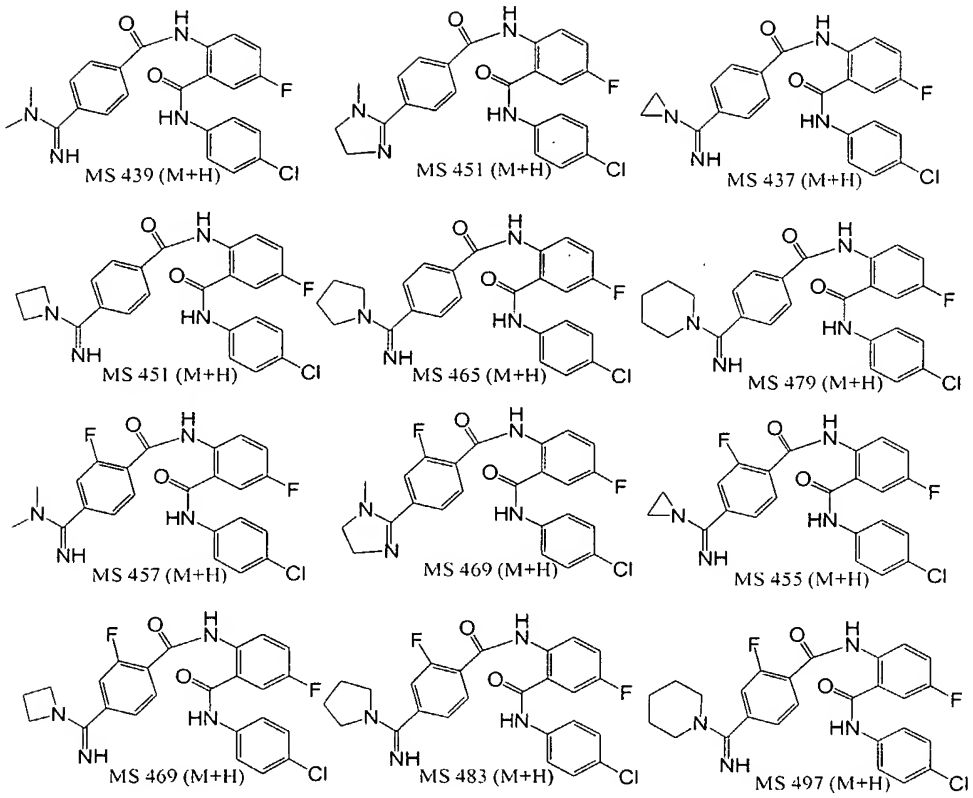

MS 481 (M+H)


MS 467 (M+H)


MS 481 (M+H)

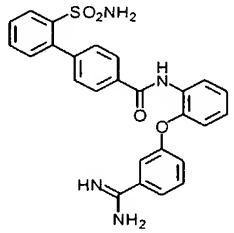

MS 495 (M+H)


MS 509 (M+H)



Example 586

3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine.



Step 1: To a solution of 2-fluoro nitrobenzene (1.41 g, 10 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (1.19 g, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (2.76 g, 2 equiv). After stirring at 60^0C for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-nitrophenoxy)benzonitrile (2.38 g, 99%). MS found for $C_{13}H_9N_2O_3$ $(M+H)^+$: 241.

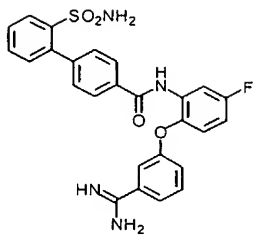
Step 2: A solution of 3-(2-nitrophenoxy)benzonitrile (1.21 g, 5 mmol, 1.0 equiv) in 30 mL of EtOH was treated with $SnCl_2 2H_2O$ (3.38 g, 3 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-aminophenoxy)benzonitrile (1.04 g, 99%). MS found for $C_{13}H_{11}N_2O$ $(M+H)^+$: 211.

Step 3: A mixture of 3-(2-aminophenoxy)benzonitrile (210 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (300 mg, 57%). MS found for $C_{30}H_{28}N_3O_4S$ $(M+H)^+$: 526.

Step 4: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine (40 mg, 83%). MS found for $C_{26}H_{23}N_4O_4S$ $(M+H)^+$: 487.

Example 587

3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

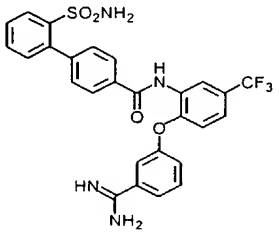


Step 1: A mixture of 3-(2-amino-4-fluorophenoxy)benzonitrile (230mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (495 mg, 91%). MS found for $C_{30}H_{27}FN_3O_4S$ $(M+H)^+$: 544.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (55 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (39 mg, 77%). MS found for $C_{26}H_{22}FN_4O_4S$ $(M+H)^+$: 505.

Example 588

3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

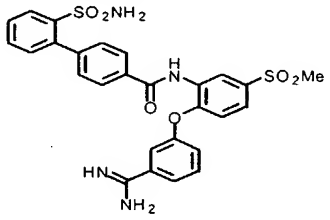


Step 1: A mixture of 3-(2-amino-4-trifluoromethylphenoxy)benzonitrile (280 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (529 mg, 89%). MS found for $C_{31}H_{27}F_3N_3O_4S$ $(M+H)^+$: 594.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (59 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (35 mg, 63%). MS found for $C_{27}H_{22}F_3N_4O_4S$ $(M+H)^+$: 555.

Example 589

3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



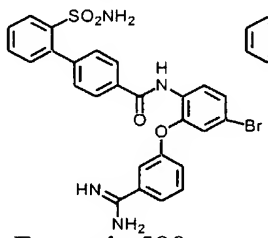
Step 1: A mixture of 3-(2-amino-4-methylsulfonylphenoxy)benzonitrile (290 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methylsulfonyl-2-(4-[(2-t-

butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (429 mg, 71%). MS found for $C_{31}H_{30}N_3O_6S_2$ $(M+H)^+$: 604.

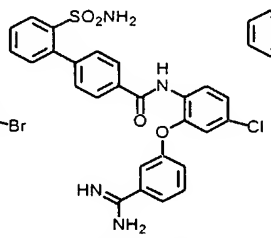
Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (60 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (27 mg, 47%). MS found for $C_{27}H_{25}N_4O_6S_2$ $(M+H)^+$: 565.

Examples 590-593

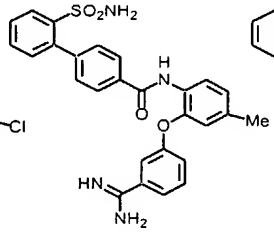
The following compounds were prepared using the procedure previously described.



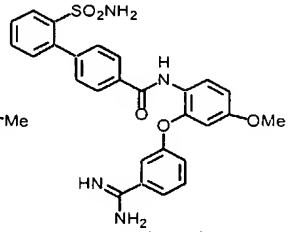
Example 590
MS (M+H):565



Example 591
MS (M+H): 521



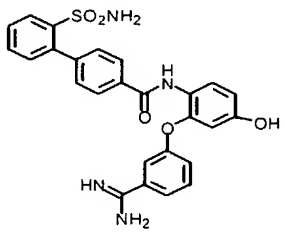
Example 592
MS (M+H):501



Example 593
MS (M+H): 517

Example 594

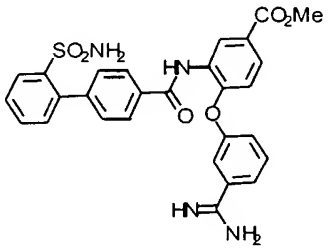
3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



A solution of 3-(5-methoxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino) phenoxy) benzamidine (52 mg, 0.1 mmol, 1 equiv) in 5 mL of methylene chloride was treated with BBr_3 (1 M in dichloromethane, 0.5 mL, 5 equiv) overnight. The reaction was quenched with water carefully and after the volatile was evaporated, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine. (41 mg, 82%). MS found for $C_{26}H_{23}N_4O_6S$ $(M+H)^+$: 503.

Example 595

3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



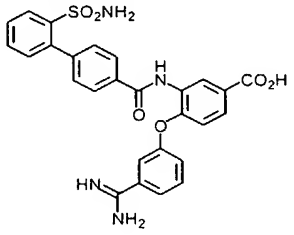
Step 1: A mixture of 3-(2-amino-4-methoxycarbonylphenoxy)benzonitrile (270 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (502 mg, 86%). MS found for $C_{32}H_{30}N_3O_6S$ $(M+H)^+$: 584.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (58 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5

equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (29.5 mg, 54%). MS found for $C_{28}H_{25}N_4O_6S$ $(M+H)^+$: 545.

Example 596

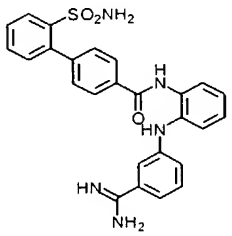
3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



A solution of 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (10.9 mg, 0.02 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (8.9 mg, 84%). MS found for $C_{27}H_{23}N_4O_6S$ $(M+H)^+$: 531.

Example 597

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine.

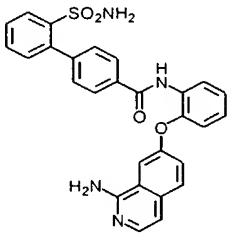


Step 1: A mixture of 3-(2-amino-phenylamino)benzonitrile (196 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino) phenylamino) benzonitrile (226 mg, 43%). MS found for $C_{30}H_{29}N_4O_3S$ $(M+H)^+$: 525.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine (27 mg, 55%). MS found for $C_{26}H_{24}N_5O_3S$ $(M+H)^+$: 486.

Example 598

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline.



Step 1: A mixture of 7-(2-aminophenoxy)isoquinoline (237 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel

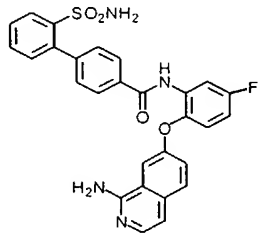
gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (469 mg, 85%). MS found for $C_{32}H_{30}N_3O_4S$ $(M+H)^+$: 552.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (110 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 2 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline (43 mg, 42%). MS found for $C_{28}H_{23}N_4O_4S$ $(M+H)^+$: 511.

Example 599

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline.



Step 1: A mixture of 7-(2-amino-4-fluorophenoxy)isoquinoline (255 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred

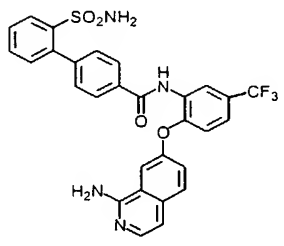
at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (467 mg, 82%). MS found for $C_{32}H_{29}FN_3O_4S$ $(M+H)^+$: 570.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (114, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline (77 mg, 50%). MS found for $C_{28}H_{22}FN_4O_4S$ $(M+H)^+$: 529.

Example 600

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline.



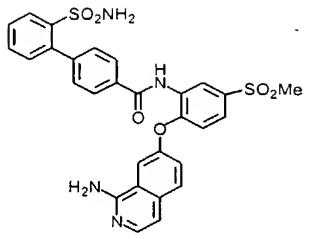
Step 1: A mixture of 7-(2-amino-4-trifluoromethylphenoxy)isoquinoline (305 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (360 mg, 58%). MS found for $C_{33}H_{29}F_3N_3O_4S$ $(M+H)^+$: 620.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (124 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried ove $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline (64 mg, 52%). MS found for $C_{29}H_{22}F_3N_4O_4S$ $(M+H)^+$: 579.

Example 601

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline.



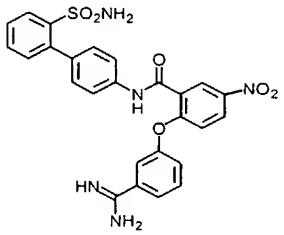
Step 1: A mixture of 7-(2-amino-4-methylsulfonylphenoxy)isoquinoline (315 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (460 mg, 73%). MS found for $C_{33}H_{32}N_3O_6S_2$ $(M+H)^+$: 630.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (126 mg, 0.2mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline (94 mg, 80%). MS found for $C_{29}H_{25}N_4O_6S_2$ $(M+H)^+$: 589.

Example 602

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine.



Step 1: A solution of 2-fluoro-5-nitrobenzoic acid (1.85 g, 10 mmol, 1.33 equiv) in thionyl chloride (5 mL) was refluxed for 2 h and evaporated. The residue was redissolved in 20 mL of methylene chloride and to the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]aniline (2.0 g, 1.0 equiv) and 5 mL of pyridine. After stirring at rt overnight, the volatile was evaporated. Flash chromatography on silica gel 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (2.9 g, 99%). MS found for $C_{23}H_{23}FN_3O_5S$ $(M+H)^+$: 472.

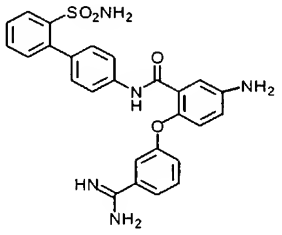
Step 2: To a solution of 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (1.18 g, 0.25 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (298 mg, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (691 mg, 2 equiv). After stirring at 60^0C for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and chromatographied to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile(950 g, 63%). MS found for $C_{30}H_{27}N_4O_6S$ $(M+H)^+$: 571.

Step 3: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (57 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed

phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (24 mg, 45%). MS found for $C_{26}H_{22}N_5O_6S$ $(M+H)^+$: 532.

Example 603

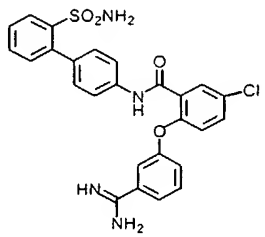
3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine.



A mixure of 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (53 mg, 0.1 mmol, 1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine (31 mg, 66%). MS found for $C_{26}H_{24}N_5O_4S$ $(M+H)^+$: 502.

Example 604

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine.



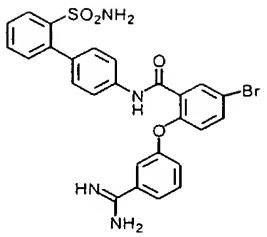
Step 1: A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (570 mg, 1 mmol, 1 equiv) and $SnCl_2.2H_2O$ (677 mg, 3 equiv) in 25 mL of EtOAc was refluxed for 2 h. The reaction was quenched with sat. $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$, filtered and evaporated to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (45 mg, 83%). MS found for $C_{30}H_{29}N_4O_4S$ $(M+H)^+$: 541.

Step 2: A mixure of t-$BuNO_2$ (21 mg, 0.1 mmol, 2 equiv), CuCl (20 mg, 2 equiv) in 5 mL of acetonitrile was refluxed for 10 min. To the solution was added 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (54 mg, 0.1 mmol, 1 equiv). The mixture was refluxed for 1h and evaporated. Flash chromatography with 1:2 EtOAc/hexane to give [(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (43 mg, 77%)MS found for $C_{30}H_{27}ClN_3O_4S$ $(M+H)^+$: 561.

Step 3: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (56 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine (47 mg, 84%). MS found for $C_{26}H_{22}ClN_4O_4S$ $(M+H)^+$: 521.

Example 605

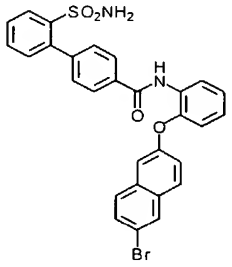
3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-bromophenoxy) benzamidine.



This compound was prepared according to the procedure described in example 19. MS found for $C_{26}H_{22}BrN_4O_4S$ $(M+H)^+$: 565.

Example 606

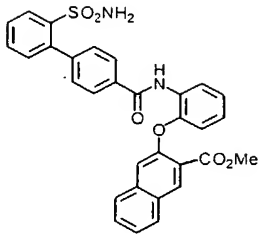
2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.



A mixture of 2-bromo-6-(2-aminophenoxy) naphthalene (314 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (378 mg, 66%). MS found for $C_{29}H_{22}BrN_2O_4S$ $(M+H)^+$: 573.

Example 607

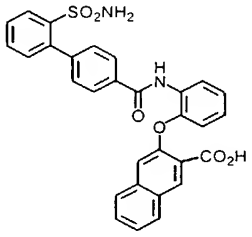
3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.



A mixture of 3-methoxycarbonyl-2-(2-aminophenoxy) (294 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (420 mg, 76%). MS found for $C_{31}H_{25}N_2O_6S$ $(M+H)^+$: 553.

Example 608

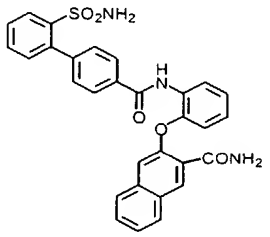
3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.



A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (55 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (47 mg, 88%). MS found for $C_{30}H_{23}N_2O_6S$ $(M+H)^+$: 539.

Example 609

3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.

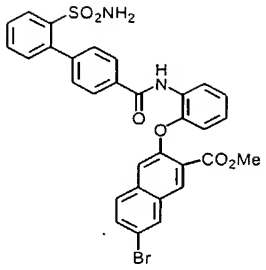


Step 1: A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (40 mg, 0.066 mmol) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, and acidified with 1N HCl until PH ~ 1-2. The product (39 mg, 100%), 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene, was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated. MS found for $C_{34}H_{31}N_2O_6S$ $(M+H)^+$: 595.

Step 2: A solution of 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (39 mg, 0.066 mmol) was refluxed in 3 mL of thionyl chloride for 2 h and evaporated. The residue was then stirred in 5 mL of 2M ammonia in methanol overnight. The volatile was evaporated and the residue was refluxed in 2 mL of trifluoroacetic acid overnight to give the product 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (14 mg, 39%) after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN). MS found for $C_{30}H_{24}N_3O_5S$ $(M+H)^+$: 538.

Example 610

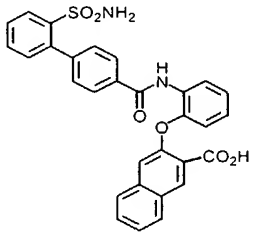
3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.



A mixture of 2-(2-aminophenoxy)-3-methoxycarbonyl-6-bromo naphthalene (372 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (423 mg, 67%). MS found for $C_{31}H_{24}BrN_2O6S$ $(M+H)^+$: 631.

Example 611

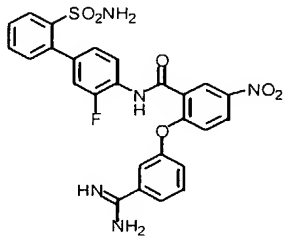
3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.



A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)-6-bromo naphthalene (63 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (47 mg, 78%). MS found for $C_{30}H_{22}BrN_2O6S$ $(M+H)^+$: 617.

Example 612

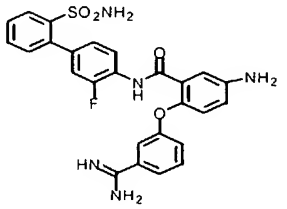
3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine.



This compound was prepared according to the procedure described in example 17. MS found for MS found for $C_{26}H_{21}FN_5O_6S$ $(M+H)^+$: 550.

Example 613

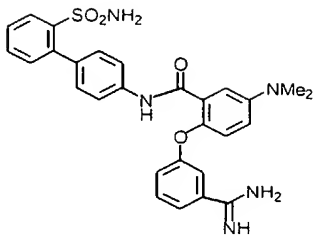
3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine.



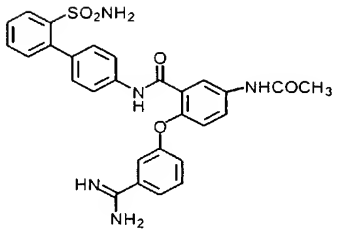
This compound was prepared according to the procedure described in example 18. MS found for $C_{26}H_{23}FN_5O_4S$ $(M+H)^+$: 520.

Example 614

This compound was obtained as a side product in the preparation of example 18. MS $(M+H)^+$: 530.



Example 615

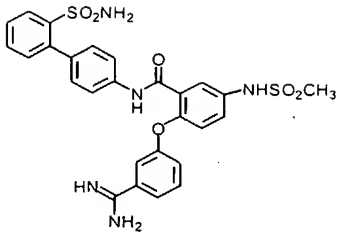


Step 1: A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (1 equiv) and $SnCl_2 2H_2O$ (3 equiv) in 15 mL of EtOAc was refluxed for 2 h. The mixture was diluted with EtOAc and washed with saturated aqueous NaHCO3. The organic layer was dried over Na2SO4, filtered and evaporated.

Step 2: The product obtained in step 1 (1 equiv) in 2 mL of pyridine was treated with AcCl (1 equiv) over night. The mixture was diluted with methylene chloride and washed with water. The organic layer was dried over Na_2SO_4, filtered and evaporated.

Step 3: A stream of HCl(g) was bubbled through a 0^0C solution of the product obtained in step 2 (1 equiv) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to the title product. MS $(M+H)^+$: 544.

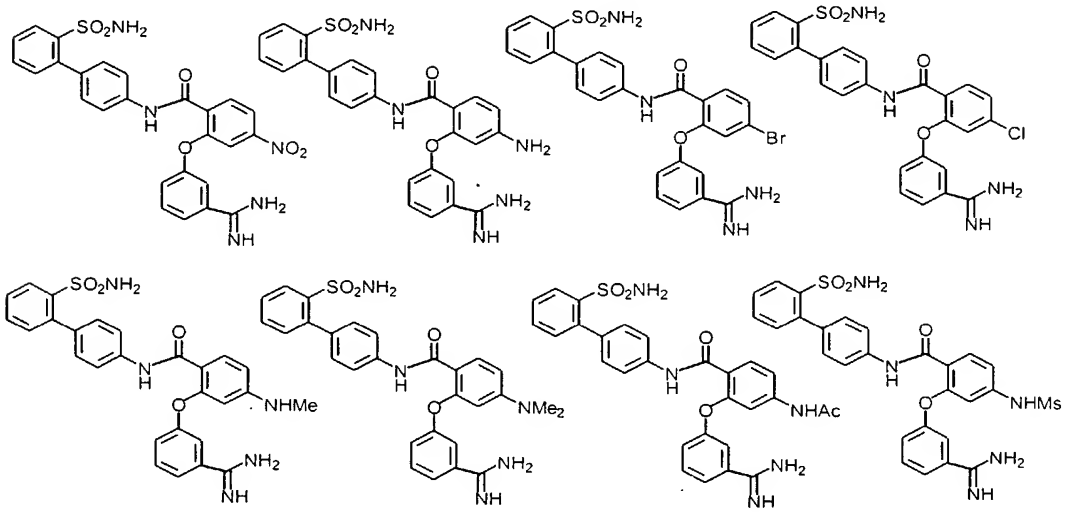
Example 616



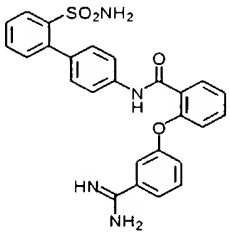
This compound was similarly made as example 30. MS $(M+H)^+$: 580.

Examples 617-624

The following compounds were made according to the methods previously described.



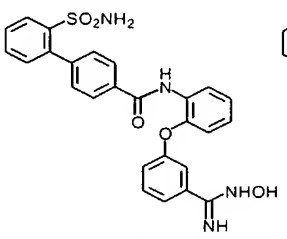
Example 625



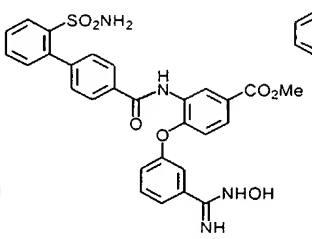
A mixure of compound 20 (1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. MS $(M+H)^+$: 487.

Examples 626-631

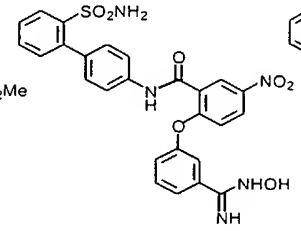
The following compounds were prepared according to the procedure described in the formation of amidines except that NH_2OH was used instead of NH_4OAc.



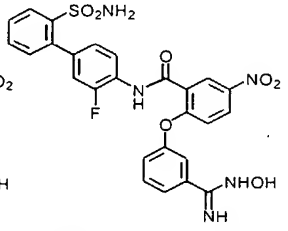
MS (M+H): 502



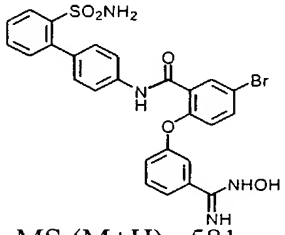
MS (M+H): 560



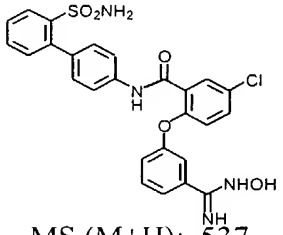
MS (M+H): 547



MS (M+H): 547



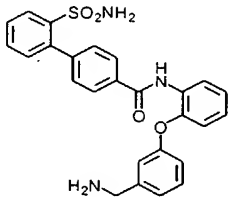
MS (M+H): 581



MS (M+H): 537

Example 632

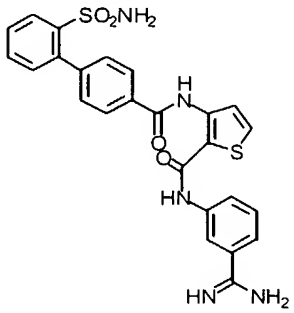
3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzylamine.



A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) benzonitrile (25 mg), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was dried on vacuum pump and then refluxed with 1 mL of TFA for 2 h, evaporated and purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. MS $(M+H)^+$: 500.

Example 633

3-[(3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl)carbonylamino]benzenecarboxamidine

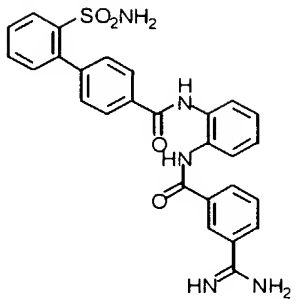


Step 1: A mixture of 3-amino-2-((3-cyanophenyl)aminocarbonyl)thiophene (1 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of the compound obtained in step 1 in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was evaporated and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. ES-MS 520 (M+1).

Example 634

3-[(3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl)carbonylamino]benzenecarboxamidine



Step 1: A mixture of 2-nitroaniline, 3-cyanobenzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

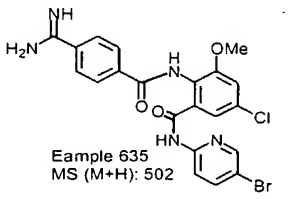
Step 2: A mixture of the compound obtained in step 1 (1 equiv) and $SnCl_2 2H_2O$ (3 equiv) in 15 mL of EtOAc was refluxed for 2 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated.

Step 3: A mixture of the compound obtained in step 2 (1 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

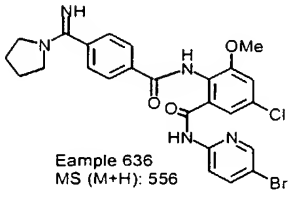
Step 4: A stream of HCl(g) was bubbled through a 0^0C solution of the compound obtained in step 1 in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was evaporated and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. ES-MS 494 (M+1).

Example 635-640

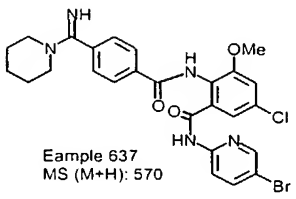
The following compounds were prepared according to the procedure previously described.



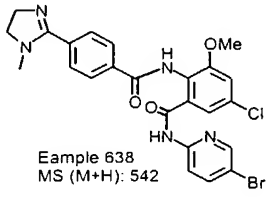
Eample 635
MS (M+H): 502



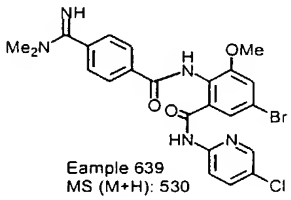
Eample 636
MS (M+H): 556



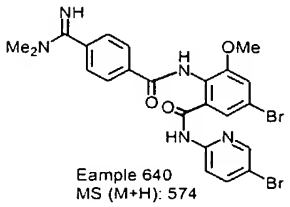
Eample 637
MS (M+H): 570



Eample 638
MS (M+H): 542

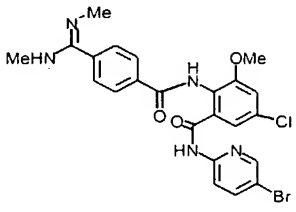


Eample 639
MS (M+H): 530



Eample 640
MS (M+H): 574

Example 641



This compound was obtained as a side product in the preparation of Example 322, described earlier, above. ES-MS 530 (M+H).

The above description and illustrative examples show numerous compounds within the formula A-Q-D-E-G-J-X which are potent factor Xa inhibitors. The description and illustrative examples also show the variety of combinations and

substituents for each group A, Q, D, E, G, J and X which may be prepared according to the invention and be useful as factor Xa inhibitors. While, for example, compounds having the same A-Q structure but a variety of substituents or D-E-G and/or J-X structures and their substituents are described and shown, the description and illustrative examples are intended to show that compounds of the invention having a different A-Q structure can also have various combinations of D-E-G- and/or J-X structures, even though such compounds may not be illustrated in the examples. In other words, each group within the A-Q-D-E-G-J-X, as each is defined above with their substituents, may be varied and combined to form sub-genuses and compounds of the invention. The description and illustrative examples show such combinations and are not intended to limit the sub-genuses or compounds within the A-Q-D-E-G-J-X genus of the invention.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED:

1. A compound of formula Ib:

A-Q-D-E-G-J-X (Ib)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -$N(R^1,R^2)$, $N(R^1,R^2)$-$C(=NR^3)$-, $N(R^1,R^2)$-$C(=NR^3)$-$N(R^4)$-, R^1-$C(=NR^3)$-, R^1-$C(=NR^3)$-$N(R^4)$-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(g) naphthyl, which is independently substituted with 0-2 R substitutuents;

(h) a monocyclic or fused bicyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CF_3, -CN, -$(CH_2)_m$-CO_2R^1, -$(CH_2)_m$-$C(=O)$-$N(R^1$, $R^2)$, -$(CH_2)_m$-$C(=S)$-$N(R^1$, $R^2)$, -NO_2, -$(CH_2)_m$-$SO_2N(R^1$, $R^2)$, -$(CH_2)_m$-SO_2R^1, -$(CH_2)_m$$NR^1R^2$, -$(CH_2)_m$$OR^1$, -$(CH_2)_m$-$C(=NR^3)$-$R^1$, -$(CH_2)_m$-$C(=NR^3)$-$N(R^1,R^2)$, -$(CH_2)_m$-$N(R^4)$-$C(=NR^3)$-$N(R^1,R^2)$, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of

halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, -$(CH_2)_{0-4}OR^5$, -$(CH_2)_{0-4}$-CO_2R^5, -$(CH_2)_{0-4}N(-R^5, -R^6)$, -$C_{1-4}$alkyl, -$C_{2-6}$alkenyl, -$C_{2-6}$alkynyl, -$C_{3-8}$cycloalkyl, -$C_{0-4}$alkyl$C_{3-8}$cycloalkyl, -$C_{0-4}$alkylaryl and -$C_{0-4}$alkylheteroaryl, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, where the hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN, -CO_2R^5, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylaryl and -C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:
a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2;

R^7 is selected from:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-O-C_{1-4}-alkyl, -C_{1-4}-alkyl-N(-C_{1-4}-alkyl, -C_{1-4}-alkyl); -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-C_{1-4}-alkyl, -C_{1-4}-alkyl);

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nOR^{2a}$, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, and a 5-6 membered

aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylaryl and -C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:
-C_{1-2}-alkyl-, -S-, -SO-, -SO_2-, -O-C_{0-1}-alkyl-, -C_{0-1}-alkyl-O-, -C_{0-1}-alkyl-N(-R^8)-, -N(-R^8)-C_{0-1}-alkyl-, -C_{0-1}-alkyl-C(=O)-N(-R^8)-C_{0-1}-alkyl, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, and - C_{0-1}-alkyl-N(-R^8)-C(=O)-N(-R^8)-C_{0-1}-alkyl-;

R^8 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-OR^{2b}, -C_{1-4}-alkyl-N(-R^{2b}, -R^{3b}); -C_{1-4}-alkyl-C(=O)-OR^{2b}; -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b}); -C_{0-4}-alkyl-C(=O)-R^{2b}; and –C_{0-4}-alkyl-SO_2-R^{2b};

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{1-4}-alkyl-CO_2-C_{0-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4

heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C_2-alkenyl or -C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(d) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused cyclic system, containing 0-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; $-CF_3$; $-OCF_3$, $-OCF_2H$, $-OCFH_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl, $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-NR^{2d}R^{3d}$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(-(CH_2)_{1-6}-N(R^{2d},R^{3d}))_2$; $-(CH_2)_{0-6}-SO_2NR^{2d}R^{3d}$; $-(CH_2)_{0-6}-SO_2R^{2d}$; $-(CH_2)_{0-6}-N(R^{5a})-C(=O)-R^{2d}$; $-(CH_2)_{0-6}-N(R^{5a})-SO_2-R^{2d}$, $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; $-O-(CH_2)_{1-6}-SO_2NR^{2d}R^{3d}$; $-O-(CH_2)_{1-6}-SO_2R^{2d}$; $-O-(CH_2)_{1-6}-N(R^{5a})-C(=O)-R^{2d}$; $-O-(CH_2)_{1-6}-N(R^{5a})-SO_2-R^{2d}$, $-O-(CH_2)_{1-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-O-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-O-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; $-N(R^{5d})-(CH_2)_{1-6}-SO_2NR^{2d}R^{3d}$; $-N(R^{5d})-(CH_2)_{1-6}-SO_2R^{2d}$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})-SO_2-R^{2d}$, $-N(R^{5d})-(CH_2)_{1-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

R^{5a}, R^{2d}, R^{3d}, R^{4d} and R^{5d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; or

R^{2d} and R^{3d}, or R^{3d} and R^{4d} taken together with the N atoms they are independently attached form a 3-8 membered saturated, partially unsaturated or aromatic heterocyclic ring;

J is a direct link or is a member selected from the group consisting of:

-N(-R^9)-C(=O)-; -C(=O)-N(-R^9)-; -O-; -S-; -SO-; -SO_2-; -SO2N(R9)-, -CH_2-; -N(-R^9)-; and –N(-R^9)-SO_2-;

R^9 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-OR^{6a}, -C_{1-4}-alkyl-N(-R^{6a}, -R^{6b}); -C_{1-4}-alkyl-C(=O)-OR^{6a}, and -C_{1-4}-alkyl-C(=O)-N(-R^{6a}, -R^{6b});

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and -C_{1-6}-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-alkyl-CN; -O-R^{2e}; -C_{0-2}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}- alkyl-C(=O)-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-NO_2; -C_{0-2}-alkyl-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; -O-C_{0-2}-alkyl-O-R^{2e}; -C_{0-2}-alkyl-O-R^{2e}; -O-C_{1-4}-alkyl-C(=O)-N(R^{2e}, R^{3e}); -O-C_{1-4}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}-alkyl-N(R^{2e})-C(=O)-R^{3e}; -C_{0-2}-alkyl-N(-R^{2e})-SO_2-R^{3e}; -CH_2-N(R^{2e})-C(=O)-R^{3e} ;-CH_2-N(R^{2e})-SO_2-R^{3e};

$-(CH_2)_{0-6}-NR^{2e}R^{3e}$; $-C(=O)-N(R^{2e},R^{3e})$; $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$; $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))-N(R^{2e},R^{3e})$; and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-2}$-alkyl-O-R^{1g}; $-C_{0-2}$-alkyl-N(-R^{1g}, -R^{2g});$-C_{1-4}$-alkyl-carbocyclic aryl; $-C_{1-4}$-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; $-C_{1-4}$-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; $-C(=O)-N(R^{3g})R^{4g}$; $-C(=O)-OR^{3g}$; $-NO_2$; $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and $-C_{0-4}$-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

3. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

4. The method of claim 4, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

5. A method for inhibiting the coagulation of a biological sample comprising the step of administering a compound of claim 1.

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/64642 A3

(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

(57) Abstract: Benzamide compounds of formula A-Q-D-E-G-J-X, where the variables are as defined in the claims, including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa are described. Compositions containing such compounds are also described. The compounds and compositions are useful in vitro or in vivo for preventing or treating coagulation disorders.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 01/06247

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/75 C07C317/44 C07D213/80 C07D213/79 C07C311/46
C07D401/12 C07D233/26 C07D295/18 C07C257/18 C07D203/18
C07D205/04 C07D409/14 C07D409/12 C07D401/14 C07D231/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 937 711 A (ROCHE DIAGNOSTICS) 25 August 1999 (1999-08-25) the whole document ---	1-5
X	WO 99 00127 A (ELI LILLY) 7 January 1999 (1999-01-07) the whole document ---	1-5
X	"Dictionary of Organic Compounds, 5th Ed., Vol. 5" 1982 , CHAPMAN AND HALL , NEW YORK, NY, US XP002161122 157909 compounds T-00160, T-00161, T-00162 page 5119 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2002	25/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

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INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 01/06247

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 C07D217/22 C07D333/38 A61K31/18 A61K31/44 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H.J. SPIE, ET AL.: "An improved synthesis of aryl sulphones" SYNTHESIS, no. 3, March 1984 (1984-03), pages 283-284, XP002161121 Georg Thieme Verlag, Stuttgart, DE ISSN: 0039-7881 compound 3c --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	T. KEUMI, ET AL.: "2-(Trifluoromethylsulphonyloxy)pyridine as a reagent for the ketone synthesis from carboxylic acids and aromatic hydrocarbons" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 61, no. 2, February 1988 (1988-02), pages 455-460, XP002161120 Japan Publications Trading Co., Tokyo, JP ISSN: 0009-2673 table 1, entry 13, product	1
X	H. SUZUKI, ET AL.: "Selective reduction with lithium aluminium hydride / diphosphorus tetraiodide" CHEMISTRY LETTERS, no. 6, June 1983 (1983-06), pages 909-910, XP002161110 Chemical Society of Japan, Tokyo, JP ISSN: 0366-7022 table 1, entry 5	1
X	J.D. YOUNG, ET AL.: "Interannular interactions in para-substituted diphenylmethane anion radicals" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 94, no. 25, 13 December 1972 (1972-12-13), pages 8790-8794, XP002161109 American Chemical Society, Washington, DC, US ISSN: 0002-7863 compound 3b	1
X	W.F. COCKBURN, ET AL.: "Molecular rearrangement of tertiary amines. Part I" JOURNAL OF THE CHEMICAL SOCIETY, no. 8, August 1960 (1960-08), pages 3340-3346, XP002161112 Royal Society of Chemistry, Letchworth, GB page 3343, line 4 - line 5	1
X	R. KAHN, ET AL.: "Addition von Maleinsäure-anhydrid an Polyene. (Über konjugierte Doppelbindungen, XIV)" BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, vol. 63, 1930, pages 2662-2679, XP002161030 Verlag Chemie, Weinheim, DE compound IV	1

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2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	W.E. BACHMANN, ET AL.: "Reduction by magnesium and magnesium halide. XII. The reaction between epoxy ketones and Grignard reagents" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 56, no. 7, July 1934 (1934-07), pages 1559-1560, XP002161032 American Chemical Society, Washington, DC, US ISSN: 0002-7863 compound I	1
P,X	D.K. HERRON, ET AL.: "1,2-Dibenzamidobenzene inhibitors of human factor Xa" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 5, 9 March 2000 (2000-03-09), pages 859-872, XP002181376 American Chemical Society, Washington, DC, US ISSN: 0022-2623 the whole document	1-5
P,X	Y.K. LEE, ET AL.: "N2-Aroylanthranilamide inhibitors of human factor Xa" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 5, 9 March 2000 (2000-03-09), pages 873-882, XP002186965 American Chemical Society, Washington, DC, US ISSN: 0022-2623 the whole document	1-5
P,X	M.R. WILEY, ET AL.: "Structure-based design of potent, amidine-derived inhibitors of factor Xa: evaluation of selectivity, anticoagulant activity, and antithrombotic activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 5, 9 March 2000 (2000-03-09), pages 883-899, XP002186966 American Chemical Society, Washington, DC, US ISSN: 0022-2623 the whole document	1-5

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (partially), 2-5

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part(s) of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the claims. The search and the report for those claims can only be considered complete for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as indicated in the relevent examples ().

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/06247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0937711 A	25-08-1999	EP 0937711 A1	25-08-1999
		AU 2623899 A	06-09-1999
		WO 9942439 A1	26-08-1999
WO 9900127 A	07-01-1999	AU 8270698 A	19-01-1999
		EP 1007037 A1	14-06-2000
		WO 9900127 A1	07-01-1999